FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Joint Meeting of Pulmonary-Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

WEDNESDAY, MARCH 10, 2010

8:00 a.m. to 5:00 p.m.

Hilton Washington DC/Silver Spring

8727 Colesville Road

Silver Spring, MD

Pulmonary-Allergy Drugs Advisory Committee

Voting Members

Paula Carvalho, M.D.
Director, Intensive Care Unit
VA Medical Center/Boise
500 West Fort Street
Boise, Idaho 83702

Jerry Krishnan, M.D., Ph.D.
Associate Professor of Medicine and Health Studies
University of Chicago
Section of Pulmonary and Critical Care Medicine
5841 S. Maryland Avenue, MC 6076
Chicago, Illinois 60637

Rodney Mullins (Consumer Representative)
National Director, Public Health Consultants
and Advocates
2960 Risen Star Court
Duluth, Georgia 30096

Thomas Alexander Platts-Mills, Ph.D.
Director, Asthma and Allergy Disease Center
University of Virginia Medical Center
Box 801355
Charlottesville, Virginia 22908

Carrie Redlich, M.D.
Professor of Medicine, Department of Medicine
Yale University School of Medicine
Occupational and Environmental Medicine Program
135 College Street
New Haven, Connecticut 06510

Non-voting Member

Richard C. Hubbard, M.D. (Industry Representative)
Senior Director, External Medical Affairs,
International
Office of the Chief Medical Officer
Pfizer, Inc.
235 East 42nd Street
New York, New York 10017

Drug Safety and Risk Management Advisory Committee

Voting Members

Judith Kramer, M.D.
Associate Professor of Medicine
Division of Internal Medicine
Duke University Medical Center
2400 Pratt Street
Room 0311 Terrace Level
North Pavilion, Room 7024
Durham, North Carolina 27705

Elaine Morrato, Dr.P.H.
Assistant Professor, Department of Pediatrics
University of Colorado at Denver
12477 E. 19th Avenue, Bldg.406, Room T09-105
Aurora, Colorado 80045

Sidney Wolfe, M.D. (Consumer Representative)
Director
Health Research Group of Public Citizen
1600 20th Street NW
Washington, District of Columbia 20009

Temporary Voting Members

Erica Brittain, Ph.D.
Mathematical Statistician
Biostatistics Research Branch, National Institute of
Allergy and Infectious Diseases
NIH
6700B Rockledge Drive MSC 7630
Bethesda, Maryland 20892

Avital Cnaan, Ph.D.
Director, Multi-Center Studies Section
Center for Clinical and Community Research
Children's National Medical Center
111 Michigan Avenue, NW, Office 5110
Washington, District of Columbia 20010

Carl D'Angio, M.D.
Associate Professor of Pediatrics
Department of Pediatrics
University of Rochester
601 Elmwood Avenue
Rochester, New York 14642

Robert Fink, M.D.
Director of the Regional Cystic Fibrosis Center
The Children's Medical Center of Dayton
One Children's Plaza
Dayton, Ohio 45404

Thomas Fleming, Ph.D.
Professor of Biostatistics
University of Washington
1959 NE Pacific Street, Room F600
Seattle, Washington 98195

William Greene, Pharm.D.
Chief Pharmaceutical Officer
Department of Pharmaceutical Sciences
St. Jude Children's Research Hospital
262 Danny Thomas Place, MS 150
Memphis, Tennessee 38105

Jesse Joad, M.D.
Professor Emerita, University of California, Davis
PI University of California Postbaccalaureate
Consortium
Sacramento, California 95817

Charles Mouton, M.D.
Professor, Howard University College of Medicine,
Department of Community and Family Medicine
520 W Street, N.W., Room 2400
Washington, District of Columbia 20059

Dennis Ownby, M.D.
Section Chief of Allergy & Immunology
Professor of Pediatrics
Medical College of Georgia
Department of Pediatrics
1120 15th Street
Dugas Building, Room BG 1019
Augusta, Georgia 30912

Susan Roberts, Ph.D.
Assistant Professor
Clinical Research Program
University of North Carolina Wilmington
601 South College Road
Wilmington, North Carolina 28403

Geoffrey Rosenthal, M.D.
Professor of Pediatrics, Director of the Hospital for Children Heart Program & Executive Director of Critical Care Services
University of Maryland Medical Center
Pediatric Department
Division of Cardiology
22 South Greene Street – N5W68
Baltimore, Maryland 21201

David Schoenfeld, Ph.D.
Professor of Medicine
Biostatistics Center
Massachusetts General Hospital
50 Stanford Street
Suite 560
Boston, Massachusetts 02114

Erik Swenson, M.D. (Acting Chair)
Professor of Medicine
Division of Pulmonary and Critical Care Medicine
University of Washington
VA Puget Sound Health Care System
1660 South Columbia Way, Room 4D142
Seattle, Washington 98108

Angelica Walden (Patient Representative)
Augusta, Georgia

FDA Participants (Non-voting)

Curtis Rosebraugh, M.D.
Director, Office of Drug Evaluation II
CDER, FDA

Badrul Chowdhury, M.D., Ph.D.
Director, Division of Pulmonary and Allergy
Drug Products
CDER, FDA

Gerald Dal Pan, M.D.
Director, Office of Surveillance and Epidemiology
CDER, FDA

Ann W. McMahon, M.D.
Deputy Director, Division of Pharmacovigilance I
Office of Surveillance and Epidemiology
CDER, FDA

I N D E X

P R O C E E D I N G S

8:01 a.m.

DR. SWENSON: Good morning, everyone. I'm Dr. Erik Swenson and I'm the acting chair of this committee meeting here, a two-day meeting of the Pulmonary and Allergy Drug Advisory Committee and the Drug Safety and Risk Management Committee.

We're here to discuss and consider the planning and design of trials to test whether the combination of inhaled corticosteroids and long-acting beta-agonist does, to some extent, mitigate a possible adverse effect of sole LABA treatment. And this design then would test the separate use of inhaled corticosteroids versus the combined inhaled corticosteroids and long-acting beta-agonist.

Before we begin the proceedings, it would be useful, I think, to have the members of the panel introduce themselves. And if we could start from my left, at the end there, we'll go through and please identify yourself and where you're from.

DR. JENKINS: Good morning. I'm John Jenkins. I'm the Director of the Office of New Drugs

at FDA.

DR. ROSEBRAUGH: Curt Rosebraugh, Director of Office of Drug Evaluation II, FDA.

DR. CHOWDHURY: I'm Badrul Chowdhury, Director, Division of Pulmonary and Allergy Products, FDA.

Dr. DEL PAN: I'm Gerald Del Pan. I'm the Director of the Office of Surveillance and Epidemiology at FDA.

DR. MCMAHON: I'm Ann McMahon. I'm the Deputy Director of the Division of Pharmacovigilance I in the Office of Surveillance and Epidemiology at the FDA.

DR. CARVALHO: I'm Paula Carvalho, Advisory Committee, University of Washington, Pulmonary Critical Care Medicine.

DR. FLEMING: Thomas Fleming, Department of Biostatistics, University of Washington.

DR. JOAD: Jesse Joad, Professor Emeritus, from University of California in Davis, Pediatric Pulmonology.

DR. ROSENTHAL: Good morning. I'm Jeff

Rosenthal. I'm a member of the Pediatric Advisory Committee. I'm a pediatric cardiologist.

MR. MULLINS: Good morning. I'm Rodney Mullins. I'm the Consumer Representative and National Director of Public Health Advocates.

MS. WALDEN: Good morning. I'm Angelica Walden. I'm from Quality Management at MCG Medical Center.

DR. OWNBY: I'm Dennis Ownby. I'm a Professor of Pediatrics in Allergy and Immunology at the Medical College of Georgia.

DR. ROBERTS: Good morning. I'm Susan Roberts. I'm an epidemiologist and Assistant Professor of Clinical Research, University of North Carolina-Wilmington.

DR. KHUC: Kristine Khuc, Designated Federal Official of the Pulmonary-Allergy Drugs Advisory Committee.

DR. SWENSON: Erik Swenson. Again, I'm Professor of Medicine and Physiology at the University of Washington, in Pulmonary Medicine.

DR. KRAMER: Judith Kramer, Associate

Professor of Medicine at Duke University, in the Division of General Internal Medicine, and I'm the current Chairperson of the Drug Safety and Risk Management Advisory Committee.

DR. BRITTAIN: Hi. I'm Erica Brittain. I'm a statistician at National Institute of Allergy and Infectious Diseases.

DR. GREENE: Hi. I'm Bill Greene. I'm Chief Pharmaceutical Officer at St. Jude Children's Research Hospital.

DR. FINK: Bob Fink, Pediatric Pulmonologist and Professor of Pediatrics at Wright State University-Dayton, Ohio.

DR. WOLFE: Sid Wolfe. I'm a general internist. I'm on the Drug Safety and Risk Management Advisory Committee. I'm from Public Citizen Health Research Group.

DR. D'ANGIO: Carl D'Angio. I'm on the Pediatric Advisory Committee. I'm a neonatologist and vaccine researcher at University of Rochester.

DR. PLATTS-MILLS: Tom Platts-Mills. I'm a Professor of Medicine and Microbiology and head of

Asthma and Allergic Disease at the University of Virginia.

DR. REDLICH: Carrie Redlich. I'm a Professor of Medicine at Yale University in Pulmonary and Critical Care Medicine.

DR. MOUTON: I'm Charles Mouton, Professor of Community and Family Medicine, Howard University.

DR. KRISHNAN: I'm Jerry Krishnan. I'm Director of the Asthma and COPD Center at the University of Chicago Medical Center.

DR. CNAAN: I'm Avital Cnaan. I'm a biostatistician. I'm Professor of Pediatrics and Biostatistics at G.W.

DR. MORRATO: Good morning. I'm Elaine Morrato. I'm an epidemiologist, from the Department of Health Systems Management and Policy, University of Colorado-Denver.

DR. HUBBARD: Good morning. I'm Richard Hubbard, the Industry Representative. I'm from Pfizer Medical Affairs.

DR. SWENSON: Thank you very much. For topics such as those being discussed today here, there

are often a variety of opinions, some of which are quite strongly held.

Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

I would like to remind everyone present to please silence your cell phones and other electronic devices, if you have not already done so.

The committee is reminded to please refrain

from discussing the meeting topic during the breaks or lunch.

At this point, I will ask Kristine Khuc, our Designated Federal Official for this meeting, to read the conflict of interest statement.

DR. KHUC: Thank you. The Food and Drug Administration is convening today's joint meeting of the Pulmonary-Allergy Drugs and Drug Safety and Risk Management Advisory Committees under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committees' compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act is being provided to participants in today's meeting and to the

public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Federal Food, Drug, and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or

minor children, and, for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussions of the design of medical research studies to evaluate serious asthma outcomes, such as hospitalizations, a procedure using a breathing tube, known as intubation, or death, with the use of a class of asthma medications known as long-acting beta2-adrenergic agonists in the treatment of asthma in adults, adolescents, and children.

This is a particular matters meeting during which specific matters related to long-acting beta2-adrenergic agonists will be discussed.

Based on the agenda and all the financial interests reported by the members and temporary voting members of the committees, it has been determined that all the interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Richard Hubbard is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Hubbard's role in this meeting is to represent industry, in general, and not any particular company. Dr. Hubbard is employed by Pfizer.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committees of any financial relationships that they may have with the firm at issue.

Thank you.

DR. SWENSON: Thank you, Kristine. I'd like now to ask Dr. Curtis Rosebraugh of the FDA, Director of the Office of Drug Evaluation, to provide opening remarks.

DR. ROSEBRAUGH: Thank you, Dr. Swenson, and good morning to everyone. On behalf of the FDA, I'd like to welcome the committee members to what I hope will be a very productive meeting.

Just to kind of set the stage a little bit for what you're going to hear over the next two days, as I probably don't need to tell you, the clinical utility and risks of long-acting beta-agonists have been a source of interest and controversy to clinicians and to us as regulators over a number of years.

So we've brought various issues associated with their use before advisory committees on several occasions, seeking you all's advice and counsel. Recently, we have announced that we are requiring manufacturers of LABA products to change their labeling based on recommendations that we received

back in the December 2008 advisory committee meeting and our own internal deliberations.

So at that meeting in December, there was a fair amount of discussion regarding the present lack of data for various safety issues. But one issue in particular stood out, and that was the lack of data regarding whether some of the safety issues associated with LABA use are mitigated when they are combined with an inhaled corticosteroid and if they are mitigated, to what degree.

Since that advisory committee meeting, I think it's fair to say there's been continuing discussion in the lay press and in scientific journals. And while there seems to be a call from many that more data is needed, there's been a variety of opinions expressed, both in the academic community and internally within the agency, as to what sort of design safety trial we need, do we need multiple trials, and what should these trials look like to answer the lingering questions that we have.

So with that in mind, the purpose of the next two days is to, again, seek your advice and

counsel on a safety trial, what it should look like to answer the questions that remain.

As you may know, Congress has given us authority under the Food and Drug Administration Amendments Act to require sponsors to conduct safety trials under certain conditions. This gives us a great deal of control in deciding the design of the trial, but it also gives us a great deal of responsibility in assuring that we identify the correct question and that we have the correct trial design that will answer a clinically relevant safety issue.

As such, we are, again, turning to you and seeking your advice in helping us to make sure we are looking at the correct issues and your suggestions in a proper trial design.

So over the course of the morning, we will be providing some background summaries, as well as reviewing the recently announced labeling concepts that the agency has required the manufacturers to make in labeling.

You're going to hear some clinical trial

considerations from the Division of Pulmonary, Allergy, and Rheumatology Products, the Office of Surveillance and Epidemiology, and the Office of Biostatistics.

I should also mention that within the last week, concerns about ethics of any further trials to obtain safety information have been raised by colleagues within the Office of Surveillance and Epidemiology, and they will also be making a presentation.

It is preferable that these issues are brought forward in time for inclusion into your briefing document so that you would have the opportunity to give them your full consideration, but we were only recently made aware of these concerns.

Following the agency presentation, you will hear from each of the sponsors later this morning and this afternoon. And then tomorrow, hopefully, after a restful evening, we will start the day off with an open public hearing and then dive headlong into a discussion of the questions.

In the briefing package, the agency put

forth a strawman protocol as a starting point for discussion, but I do want to emphasize that that's just a strawman and it's just to give us a place to start at. We are not wedded to anything at this moment.

With that as a background, I would, again, like to say that I appreciate the time that everybody has taken out of their busy schedules, because I know how busy we all are. And I think it is, again, a tribute and a testimony to the importance of this issue and to you all's dedication to public health that you're helping us out with this.

With that, I'll turn it back over to the chair.

DR. SWENSON: I have to remind everyone to please turn on your mic when you wish to speak. I'd like to ask Dr. Badrul Chowdhury of the FDA to begin their presentation.

DR. CHOWDHURY: Good morning. I'm Badrul Chowdhury. I'll be speaking to you for the next 35 minutes or so, talking about long-acting beta-agonist safety trials, as Dr. Rosebraugh mentioned.

Here is the outline of my presentation. I plan to use a couple of slides to briefly talk about asthma in general terms and, also, point out some specific epidemiology aspects that may have bearing and implication on the trial design that we're talking about.

Then I'll delve into the background of the FDA decision for long-acting beta-agonists for asthma. And I will go a bit into science and old clinical trials; talk very briefly about the last advisory committee that Dr. Rosebraugh mentioned that occurred in December 2008; and, give you some reasoning and rationale for the FDA decision.

The intent here is to put all of us on the same page, because some of you may not have been here at the last advisory committee. And then I'll talk about the design elements of the safety trial, which is our strawman design for you to consider and discuss upon.

So with that background, let me talk over asthma with the next couple of slides. As we know, asthma is a chronic inflammatory disease of the

airways, characterized by varying and recurring symptoms of shortness of breath, chest tightness, wheezing, cough, and airflow obstruction.

They are categorized as intermittent or persistent, with three sub-classifications under persistent, and these are detailed in various documents, such as the NAEPP expert panel report and other documents.

Now, patients with asthma can vary from time to time under severity; and, therefore, there is really no effect to classification of disease or treatment for a fixed classification, but rather it changes with time.

Here is some morbidity and mortality data relevant to asthma. It's a pretty common disease and based on a 2008 WHO report, the worldwide prevalence is approximately 300 million and the ranges vary from country to country, going from 1 percent to 18 percent.

In the U.S., based on the 2008 CDC report, the prevalence of asthma for adults is 7.3 percent, or 16.4 million, and for children, it's 9.4 percent, or 7

million. In the U.S., the hospitalized care for asthma, based on the CDC report, is 444,000, where the hospital discharges, the first diagnosis listed was asthma. And the hospitalization here was for an average of 3.2 days.

The mortality for asthma, as we know, in the U.S. over the last couple of years is coming down. The number of deaths is just over 3,500 and the deaths per 100,000 population is 1.2.

A couple of points for you to consider. As far as the racial demographics and distributions go, the prevalence of the disease is much higher in African-American or blacks compared to whites. And hospitalization, mortality, is also high in that age group. But death, which we're talking about as we talk about the design and conduct of clinical trials, in asthma occur in two situations, hospital and out-of-hospital.

Most of the deaths in asthma are in patients who are poorly controlled and have possibly predictable measure and could be prevented. But, again, many of the deaths in patients with asthma

occur in an outpatient setting, with really no clear signal of a person having serious or severe asthma and risk of death.

There is not really a close co-relationship between hospitalization and death. In other words, the link between the two may or may not be there.

Here is a very broad list of medications for the treatment of asthma. I will not read the list. This is in your briefing document and similar lists are also available in various publications. I'm quoting here the NAEPP report.

Among the various classes of drugs for treating asthma, the main drugs that are commonly used in adults and adolescents are bronchodilator, beta-agonists, either short-acting or long-acting, which we're talking about today, and inhaled corticosteroids.

Another large group of drugs that are used primarily in pediatrics falls into the category of leukotriene-modifying drugs, montelukast being the most common example of this.

Here is a list for the long-acting beta-

agonists that we will be talking about today and tomorrow, and this is just a list listing the various active ingredients and the products.

Under formoterol, there are two, which are in square brackets, because these drugs are formulated as inhalation solutions for use in nebulizers and the specific reason why they're in parentheses is because they do not carry an asthma indication. Their indication is for chronic obstructive pulmonary disease, or COPD.

The FDA decision and the labeling changes that I will elaborate subsequently further are for the treatment, chronic, of acute asthma. Prevention of exercise-induced bronchospasm, or EIB, is not impacted and not discussed here. And as I mentioned earlier, COPD, which some of these drugs carry, is, again, not impacted and not discussed here.

Here is a very high level summary of the FDA decisions on long-acting beta-agonists that was made on February 18th and there is a reference, if you're interested, for further details.

On a very high level, the four concepts, the

first one is that all long-acting beta-agonist products will retain the asthma indication and we believe the benefits of long-acting beta-agonists continue to outweigh the risks when the drugs are use appropriately and they should remain available for the treatment of asthma.

You have seen the list of drugs for treatment of asthma and, as you can appreciate, the number is quite limited and the alternates, which can become alternates if LABAs are not available, are not safe either and have their own risk profiles. And by these, I mean drugs such as oral steroids, theophylline, and immune-modulating drugs, such as anti-IgE.

We have some professional labeling changes and safe use initiatives that I will cover subsequently. And the point here is, in general, the use pattern of long-acting beta-agonists perhaps need to be thought over and see if the drug is used in excess or not. And the labeling changes that I will show later on, the concept here is intended to try to use long-acting beta-agonists appropriately to

patients who truly require them, and those would be patients with asthma that cannot be adequately controlled with asthma control medication, such as inhaled corticosteroids.

We also announced that the manufacturers of long-acting beta-agonists conduct large clinical trials to evaluate the risk of addition of long-acting beta-agonists to ICS, and this is the reason why we're here today, as Dr. Rosebraugh mentioned.

Just to go over the background of this FDA decision and multiple public meetings in the past and journal and other publications, it's really a judgment on the risk and benefit of the creation of this class of drug.

The risks that we are discussing and dealing with are serious asthma exacerbations resulting in asthma-related death, intubations, and hospitalizations, and this has been discussed extensively.

On the benefit side, these are beneficial drugs and provide symptomatic benefit for improved lung function, such as airflow measures, peak flows,

and FEV-1, and they also do reduce nighttime awakenings for asthma symptoms and do decrease the use of rescue short-acting beta-agonists for asthma exacerbations.

The risk-benefit assessment for long-acting beta-agonists and short-acting beta-agonists are probably quite similar and this is not surprising, because the two classes of drugs have similar basic pharmacological activity and clinical effects, except for the duration of action, long-acting beta-agonists having a duration of action of 12 hours or longer.

Neither short-acting beta-agonists nor long-acting beta-agonists have any apparent clinical anti-inflammatory properties.

In the next couple of slides, I will review data at a very high level, but relevant for the safety that we're talking about here and efficacy for these beta-agonists, both short and long.

Then I'll come back to the FDA recommendations and put the recommendations on the table for you to understand what those recommendation concepts are and how they may or may not potentially

impact future asthma clinical trials that we're talking about today.

I'll use a pretty old slide to make some points that this beta-agonist controversy is not new and goes back over 50 years, starting with the early introduction of these drugs in the world market, going to the 1920s and '30s.

In this slide, I'm showing, on the horizontal axis, years; on the vertical axis, asthma attack per 100,000. And these are population studies from various countries, such as New Zealand, England/Wales, and the Netherlands.

The drugs which have come up over multiple years as having risks of asthma-related deaths are older drugs such as epinephrine, which hardly is used for asthma in this day and age; isoproterenol, another drug of the class, and other formulations of isoproterenol. And these drugs, as we know now, are nonselective and, not surprisingly, they have been linked with asthma-related death.

Somewhat recently, fenoterol, which is a short-acting beta-agonist, again, somewhat

nonselective, had been linked with asthma deaths in various countries, primarily New Zealand and, also, in European countries, and has been extensively evaluated, resulting in multiple publications on that.

Currently, in the U.S. and most other countries, the primary short-acting beta-agonist, for all practical purposes, is albuterol. So from here on, when I talk about short-acting beta-agonist and albuterol, I'll be using the terms interchangeably. The major drug is albuterol.

Now, data on albuterol, as far as the safety/risk is concerned, is somewhat limited. But, again, there are many publications showing risk of albuterol in causing asthma worsening and asthma exacerbation.

One study in that respect that gets quoted quite a lot and has had some impact in the current management of asthma is a case controlled study published in the New England Journal of Medicine a couple of years ago, where about 12,000 patients who had asthma medications between 1978 and 1987 were looked at.

The intent primarily in this study was to look at the risk for fenoterol and really see if the risk applies across other areas. And I'm putting some quotes here from the results of the article; that for death from asthma, use of the beta-agonist fenoterol was associated with an odds ratio of 5.4 as compared with 2.4 for the beta-agonist albuterol. It was comparative between fenoterol and albuterol, fenoterol showing the higher risk. And there's some calculations done in the study.

It was concluded that on a microgram equivalent basis, the odds ratio for the same outcome for the two drugs essentially was similar, 2.3 for fenoterol and 2.4 with albuterol, meaning that if this drug is used in excess or in high amounts, the risk will be there.

Again, at that time, there were controversies around this issue, which, at this time, is put to rest. But just to point out the controversy, I'm just putting out one conclusion from an article that was published in the JAMA a long time ago, pointing out the controversies at that time, stating

that these are extremely small effects, possibly related to mode of delivery, specifically, nebulizers.

They also went on to say that the findings that came out of the study, which resulted in a lot of headlines, are misleading. So these controversies played out over the years and with initial publication of the long-acting beta-agonist studies, we saw somewhat similar.

Now, going back to one more slide and talking about the albuterol and see where we are. To address this controversy, there were a couple of studies done, and I'm putting out two studies here, one from the U.S., the BAGS study, one from the U.K., the TRUST trial, and the intent of both of these were to look for if chronic use of albuterol actually causes worsening of asthma or asthma death.

The BAGS study, which was funded by the NHLBI's Asthma Clinical Research Network, published in 1996, looked at over 200 patients, over 16 weeks, when they were given chronic albuterol treatment, and the primary outcome was trough airflow measured as peak flow. And the findings came back really as neutral,

showing no beneficial effect nor worsening of asthma.

The other trial, which was conducted in the U.K., which was published in 2000, basically showed the same finding. And this trial was substantially larger, involving just under 1,000 patients and given albuterol in a dry powder inhaler formulation around the clock, and had patients stratified based on background steroid use as no use, meaning background medicine-none; moderate use, background medicine up to 800, and higher dose over 800 to 2,000. And this was a one-year long study and, again, came back as neutral, showing no beneficial or harmful effect.

Again, given the long association of beta-agonists with worsening asthma and asthma death, rightfully, the scientific community decided -- and it is the practice of medicine now -- to use beta-agonists as less as possible, suggest albuterol to be used only on an as needed basis, and use asthma control medications when patients are using a lot of albuterol.

A couple points here, that we had known for a long time that short-acting beta-agonists can worsen

asthma and cause potentially harm. And, again, we have seen studies such as these exposing patients to albuterol around the clock for over a year, which was done quite safely.

Over the last couple of years, as you know, albuterol and other beta-agonists and other inhaled medications are being reformulated in the U.S. It has been done to free them of the purple MCFC (ph). And for these reformulated products, we have seen many control studies giving albuterol around the clock in a controlled fashion pretty safely.

Now, salmeterol, just to, at a very high, touch the data, I will not go into these. These are published. It has been discussed extensively in meetings such as this and other places.

The risk for salmeterol was known even before Serevent was approved in the U.S. in 1994. Recall the albuterol studies, which I showed, were done in the late '90s and 2000. And around the same time, there was another study which was going on in the U.K., the SNS trial, comparing salbutamol or albuterol to Serevent or salmeterol, a pretty large

study, involving over 25,000 patients in a 2:2:1 randomization.

The study showed a signal of asthma death, with a relative risk of 3, with a p value not significant. And after salmeterol was approved in the U.S., there were reports of worsening asthma and asthma death, and, based on these, developed the signal further.

The manufacturer of salmeterol conducted the study, which we have heard multiple times, the SMART trial, which basically confirmed the findings and showed an increase in asthma death with salmeterol compared to placebo, with a relative risk of 4.

Again, for the formoterol, we discussed this at the last advisory committee. I'm just going to lay out, at a very high level, what we knew. There are no large control studies and association comes as a class effect, confirmed by actually smaller studies with formoterol. And during the development, these smaller studies showed worsening of asthma, as asthma exacerbation requiring intubations. And we have published that in an article which we also discussed

here.

The combination product containing formoterol and budesonide also had similar findings, which we discussed here. And the similar findings were in the arm where the salmeterol was used as a single entity, as a single-ingredient product.

Now, I would like to take a few minutes and spend some time on this slide and talk about meta-analysis. We have discussed meta-analysis quite extensively at our meeting here in 2008 and many meta-analyses are published.

On the question about a single-ingredient long-acting beta-agonist, basically, the meta-analysis confirms the safety risk. And this is not a surprise, because the vast majority of data at the end for this meta-analysis is coming out of the SNS and SMART trials. So it shows the same signal.

The other is in combination with inhaled corticosteroids and, again, some suggest decreased risk, while others do not. And the issue with meta-analysis, it becomes how one looks at them, what trials are included in the meta-analysis, what trials

are not.

Some meta-analyses showing safety risk in combination with corticosteroids may include some studies and not others. So, really, whether meta-analysis answers this question is an open question by itself and the general consensus is that it does not and we need more trials to answer the question.

Now, on the last advisory committee meeting, the FDA presented FDA's meta-analysis, which has generated some interest, and you will see the same meta-analysis data being presented today. And actually, the same meta-analysis data also appeared in a prospective article in the New England Journal of Medicine, which was published soon after the last advisory committee meeting.

To draw your attention to the meta-analysis, I would ask you to look at the FDA briefing document, on page 3, which is somewhat in the middle, and the slide number is slide number 6. The same also appears later on a page 7. And this is the figure showing the meta-analysis and the increasing risk with decreasing age.

I would like to point out that this meta-analysis is presented as a risk difference. And if you look at the point estimates, it shows a remarkable trend, with increasing risk with decreasing age.

The point estimates in the slide that I am asking you to look at go from minus 3.56 for age 65 to 2.13 for slightly older patients, 5.57 for ages 12 to 17, and 14.83 for ages 4 to 11.

DR. D'ANGIO: I'm sorry. What are you looking at? What slide, please?

DR. CHOWDHURY: I'm looking at the FDA's background document and I'm referring you to a slide, which has got the number slide 6. If you look at the page number, you will see the page number 3. On the left-hand slide, there are two big slides. The top one is background. On the right-hand side, in the second portion, is a slide titled "Age Trend."

Let me just move on. If necessary, we can come back to this topic with some backup slides.

DR. SWENSON: Dr. Chowdhury, it's on page 20 of this.

DR. SCHOENFELD: If you look at page 19 and

then keep going, it's after that.

DR. CHOWDHURY: Thank you very much. Okay. So that is the figure I was referring to. Thank you.

So one point, too, that I wanted to make here. This really is a risk difference and I would be cautious how this is interpreted, and I hope it is not being interpreted as a risk ratio.

Again, there is some baseline imbalance of events. The event that was driving this meta-analysis is primary hospitalization. And because of the baseline imbalance, one can look at this in various of ways.

I'm just pointing out an ultimate way to look at it might perhaps be risk ratio. And if we look at this with risk ratio, the differences may not be as remarkable. And some rough calculation, if you do it by risk ratio, the point estimate would be actually much different.

For ages 65 and higher, the rough calculation would be approximately .7; for ages 18 to 64, it will be 1.24; for ages 12 to 17, it will be 1.7; for ages 4 to 11, it will be 1.72.

So, again, I'm pointing out these meta-analyses as not really as complementary perhaps as hypothesis-generating and depending how you look at it, it can come back with different conclusions.

So let me move on and talk a bit about the possible mechanism. And the bottom line here is that the mechanism is not known. And people have speculated various contributing factors, which we have known, given the history with other beta-agonists, that higher doses are associated with more risk; less selective beta-agonist probably causes more risk.

It's hypothesized that the beta-agonist on board can reduce protection against bronchoconstrictor stimuli or may mask symptoms of worsening asthma.

In the future, at some point, we may actually find some markers, which we are not there yet. And we know that the mechanism for long and short-acting beta-agonists are probably the same, given the similar mechanism of action and clinical effects for these drugs.

Just putting up the current asthma treatment guidelines, because I think we'll be coming to this as

we discuss the clinical trials; so that, again, we are on the same page on the current asthma treatment for ages that I'm showing here, 12 and above and 5 to 11.

I will not go through the steps here. This is for you to see. The high level points I want to make here, that for intermittent asthma, which is step 1, which is really mild asthma, the treatment really is a short-acting beta-agonist, such as albuterol, as needed.

As asthma becomes more severe, I'm talking about persistent asthma, the treatment goes up stepwise from step 2 to step 6. And if you look at these treatment options, the basic thing that you will see is use of a corticosteroid across, which is the anti-inflammatory drug and asthma control medication; and, second, you will see other drugs coming on and one other drug that comes on in step 3 onwards is a long-acting beta-agonist.

So this is the current asthma treatment summary. And, again, the idea for asthma treatment is to stepwise treat the patients, with the stepping up as needed and stepping down as needed, based on asthma

control. And the timeframe for step-down is approximately 3 months after assessing patients.

Later on, I'll talk about the labeling concepts and I just want to use this slide to point out the way we are interpreting this and the way our recommendation would stand.

First is we are recommending that long-acting beta-agonists be used later in more severe patients, when they actually truly need a beta-agonist for long-term control, more or less, pushing it toward the right-hand side. You will see the long-acting beta-agonist is step 3 onwards.

The current concept of step-down is more on the steroids; here, high dose oral steroid, and high dose, mid dose, and low dose. And the point that we are raising is perhaps to also consider stepping down a long-acting beta-agonist, where appropriate.

Now, these NAEPP and other guidelines recommending long-acting beta-agonists came from a variety of studies which are published in literature and elsewhere, and, again, we discussed this at the last advisory committee meeting and I'm just pointing

out some studies here, just some selective studies, as examples that have tested long-acting beta-agonists, along with corticosteroids, in various control settings, some of the studies going over a year.

Like, the FACET study was a 1-year study; SLIC and OPTIMA study was a 6-month study. And we are seeing the recent pediatric study, called BADGER, which is in the online version. And these studies have used long-acting beta-agonists on a chronic dosing regimen, with a background corticosteroid, for a long time period. And when we discuss our study design, please keep these studies in mind.

On the efficacy side, these studies have been taken as examples, meaning better asthma control, that it can be achieved by using long-acting beta-agonists, along with a corticosteroid. And one point to note, that these benefits that were shown by adding long-acting beta-agonists were benefits which were largely driven by beta-agonist effect, such as airflow and reduced short-acting beta-agonist use.

So from the efficacy standpoint, there may be perhaps more to desire, but that was the efficacy

basis and we do acknowledge that there are no studies that have shown that long-acting beta-agonists alone or in combination with an ICS increases survival or positively impacts severe asthma exacerbations.

Now, this controversy about long-acting beta-agonists -- and, historically, as I showed you earlier beta-agonists -- has gone on for years. And as we have discussed here, we had multiple advisory committee meetings, multiple opinions and views in various journals, including some that I'm showing here, and this is ongoing.

So at the last advisory committee, again, just to put you all on the same page, what was discussed, what was the conclusion in the December 12th advisory committee -- December 2008 advisory committee, which was a large meeting such as this, where we had three committees participating.

As a conclusion, I just wanted to point out just one question and the responses, but you understand what recommendation was given and how we moved forward. It was a question for these four products -- single ingredient and the combination for

the two beta-agonists, salmeterol and formoterol, with their corticosteroid combinations.

The question is, does the safety outweigh the benefits for the maintenance and treatment of asthma for patients, and the question builds on basically the labeled recommendation or the treatment guideline recommendations, which were, more or less, at that time, in parallel. And the question was broken down in ages.

So the fundamental question was a risk-benefit assessment for the maintenance and treatment of asthma. And here is the summary vote. I will not read every line. This is in the print for you to see. But the voting and the recommendation that we got was essentially a negative for single-ingredient products, with the "nos" being major and the number of "nos" increasing with decreasing age. For the combination product, it was generally favorable; but, again, for the pediatrics, there were some concerns.

So before going on to the clinical trial, I just wanted to bring up for your awareness the labeling concepts and how these may or may not impact

the control trial that we're talking about.

The four labeling concepts, which are listed here, that we are putting out in our decision, first, is to contraindicate the use for single-ingredient long-acting beta-agonist for all patients.

Second is, if possible, discontinue long-acting beta-agonist once asthma control is achieved and maintain patients on long-acting beta-agonist, such as inhaled corticosteroids.

Third, recommend against using long-acting beta-agonist in patients whose asthma can be adequately controlled on low or mid-dose steroids. And, finally, for the pediatric patients, for ages 18 and below, for issues of compliance, recommend using a fixed dose combination product.

Let me outline briefly the goals of these, so that we understand where we are. The first goal is assure that long-acting beta-agonists are used correctly, which is with a control medication, such as ICS, and these are listed here. And this is really not controversial and it is the way that drugs mostly are used or should be used.

The other is to reduce the overall long-acting beta-agonists. The reasoning is if this class of drug is associated with a safety signal, then the use should be appropriate and not in excess.

This is a new labeling concept and I had mentioned about this when I was showing you about the stepped-down and stepped-up treatment of asthma, recommending that the step-up happen later and the step-down for LABA happens earlier.

Now, one question that comes up on the use of this product safely, whether concomitant use of inhaled corticosteroids mitigates safety risk, and this is actually an unanswered question and probably an unanswerable question. And I do not think one can reasonably do a study to precisely answer the question.

We do, of course, need control data and the question is to evaluate the risk of adding LABA to an ICS, and that's what we're discussing here today.

At the last advisory committee meeting, which I alluded to earlier, there were pretty large discussions and there was a voice that more data is

needed. And one of the decisions that we made, which I alluded to earlier, is requiring additional safety trials to be conducted in adults and children containing these products, and this is where we are today.

So I'll go over, in the next couple of minutes, our strawman proposal for the safety trial, and this is, again, to generate discussions and interest and we are not necessarily wedded to any concept.

The objective of the safety trial will be to determine the safety of long-acting beta-agonists added to inhaled corticosteroids alone for the treatment of asthma. So, in essence, the treatment arms become LABA plus ICS versus ICS alone.

A secondary objective that we're putting up is efficacy, the reasoning being that it would be unattractive to patients and other interested parties to do a safety-alone study without an efficacy measure.

On the other hand, we also need to be cognizant and careful what that efficacy measure

should be or could be, because doing airflow in this large study is probably not tenable and we know the airflow benefit will be shown, whether quality of life or other patient-centered benefit may be looked at, and, again, this is up for discussion in the committee meetings.

Now, of the products that are undergoing consideration, again, potentially all, and this is the slide that I'm listing all the long-acting beta-agonists either as single-ingredient products or as combination products for you to discuss and deliberate upon.

We think there's enough data with single ingredient, Serevent, and for the Advair, the multiple products, there is one Diskus and one formulation. So, conceptually, one can think about using three products -- the combination product, Advair as a Diskus, and not all three, the reasoning being this one has an age which goes to the younger patients and all of these products contain some matter of -- is made by the same manufacturer and the exact product for the Diskus and the Advair Diskus are the same,

except in the active ingredient.

However, we do think that separate studies should be done for the two formoterol products, the single entity and the combination product. These are made by different companies.

The formulations are very different, one being a dry powder inhaler delivered by a dry powder inhalation device, the other one being inhalation aerosol in an HFA formulation. And there's not really any strong pharmacokinetic or pharmacodynamic data for one to look at and conclude that the formoterol for both these products are identical.

So, conceptually, then, again, to consider the three products to look at for trials are Advair Diskus, Foradil aerolizer, and Symbicort inhalation aerosol.

The hypothesis primarily is the addition of LABA to ICS in patients in moderate to severe asthma does not increase the risk and we think it is to be a randomized, blinded, controlled trial. On this point, maybe we are more formal that it needs to be answered in a blinded, controlled trial and not epidemiological

observations.

We'll hear a lot about non-inferiority margin and the numbers around that in a subsequent presentation. Again, I'll defer that discussion for the subsequent presentation. But, also, we need to be careful in keeping our thinking of how large a study is feasible and when does it become that a very large study to answer the question is so large that perhaps the safety risk is so small, it may not necessarily matter.

So one has to be practical and, again, scientifically correct and accurate.

The safety endpoint, ideally, could be asthma death or should be asthma death, but, again, this is not a common event and a sample size may be prohibitively large and cannot be done.

The composite endpoint is something that we're putting forward for you to consider and we think for patients 12 and older, the composite would be asthma death, asthma intubation, and asthma hospitalizations as a composite, again, fully acknowledging and understanding the limitations of

this, that death and intubation may not necessarily be predictive of hospitalization and hospitalization may not be predictive of death. But, again, these are real endpoints that may matter.

For pediatric patients, death and intubation are rare events. So we think hospitalization is perhaps the single entity to look for.

The age ranges need to cover all relevant ages, meaning the approval of the product down to whatever age that be, which is 4 years as a class. Two options to consider for this are two studies, one for patients 12 years and older and the second one for patients 4 to 11.

Note that we are including 12 to 18 within this one study, 12 and older, because patients 12 to 18, in most of the cases, for asthma, behave similar to patients 18 and older and most of the development program for asthma has gone under 12. And the SMART study, which we discussed earlier, had gone down to age 12.

The other option is one large study, yet larger perhaps, with stratifications covering all the

ages. And another point to consider along with age is, of course, race, and we have a question to that and I also mentioned earlier that asthma mortality, morbidity is perhaps higher in African-Americans than others. So that race subgroup needs to be adequately represented. The question is what is adequate.

So the drug products and number of studies, I'm just putting it out assuming two studies. If it is one study, the dynamics are different here. For ages 12 and older, we think Advair Diskus 250/50 or 500/50, maybe 250/50 is the right one, again, up for discussion, comparing to the corresponding doses of fluticasone given in the same device at the same doses.

For the formoterol, Symbicort, which is a commercial product, compared to budesonide in the same device, same formulation, and the budesonide would be experimental.

For Foradil, this would be freestanding, because there is no fixed dose combination product, meaning the beta-agonist and the steroids are given as two separate inhalers.

For ages 4 to 11, it's just one product, which is Advair Diskus, and we think the right dose is a lower dose. That's the dose appropriate for children.

As far as treatment comparisons, one can look at it in different ways, and this is something that we would like you to consider and deliberate upon tomorrow, is what could be the treatment options. I mean, one can look at it in various ways and I'm just putting out three ways. There may be more than three.

I'm using Advair 250/50 as an example. One can be a fixed-dose ICS, meaning that the Advair and the Flovent is fixed. Second is potentially three options. One is to have a high dose of a steroid. Third is a real life situation where the steroid is variable.

Each of these has this pro and con, and just a point or so. This one, for example, probably will give the cleanest result as far as interpretability is concerned, because the dose of steroid is fixed. The question that comes is how feasible it is, how long does the study go on.

On the fixed dose, with three, it gives the opportunity to compare what happens adding a beta-agonist versus increasing the steroid. Interesting question, but, again, the study becomes larger, with three arms.

The variable dose, in some way, may be attractive, because from a patient standpoint, the patients are on a variable dose, so the steroid arm is going to be up and down. The problem becomes what happens if the steroid ends up being different than what the comparator is, how do we compare them.

So this is what we're pointing out for you to consider and think and give us your best advice. One can even think about other options other ways, including even combining some of these, for you to think about.

The duration of studies, again, the subsequent presentation that you will hear is based on a 12-month, again, for the number calculation, larger, needs less patients, the problem becomes logistics. Six months is another option, given the SMART study example.

Another option is even going shorter, 3 months. Again, for you to discuss and give your opinion on. And each of these has their own advantages and disadvantages.

Let me just touch on the new labeling concept and point out how it may or may not -- for us, may not -- impact the study that we're talking about. The first concept was to contraindicate use of LABA with other steroid, which is pretty straightforward. That's the way most of the treatment recommendations and guidelines are. And the trial that we are proposing here does not have a single-ingredient long-acting beta-agonist arm. So this concept is not applicable from any standpoint for this design.

Second is stop long-acting beta-agonists, if possible, and this is something, again, for you to discuss. And our point is that these are labeling recommendations and, again, one can address actually doing a longer-term study putting patients on long-acting beta-agonists longer, because these are control trials and patients have appropriate escape mechanisms if necessary to protect patient safety.

Again, one can choose populations and patients where a longer-term treatment may be appropriate or desirable. And, again, pointing out studies which I pointed out earlier, the long-acting beta-agonist plus ICS trials and albuterol trials and others, long-term studies with these drugs, even knowing what the safety risks are, have been done quite safely in a control situation.

Again, this is a point to consider, but we do not think it is a serious impediment for doing future studies.

The same applies here, which is the concept is recommend against using LABA in patients whose asthma is adequately controlled on low and mid-dose steroids. Again, the population that we selected, which is appropriate for doing a study, where these steroids in high dose may be appropriate.

The final labeling point, which was a fixed dose for combination products, is, again, not necessarily very much applicable for continuing the studies, because we are asking this labeling concept to assure compliance. And in the studies, patients

will be given a combination product.

So in conclusion, I'd just like to thank you for your time. And the point here is that we need data from randomized, blinded, control trials and we have presented here design elements of a safety trial purely for your interest and not necessarily we are wedded to anything.

We really except and look forward to having a consensus-building here with experts sitting across the room and give us a recommendation that we can take and we can hear in designing a study which will be appropriately designed and answer the question that we're trying to ask here.

Thank you very much.

DR. SWENSON: I'd like to ask Dr. Ann McMahon, the Deputy Director of the Division of Pharmacovigilance, to continue the discussion.

DR. MCMAHON: Good morning. It's a pleasure to speak with you today about study design considerations for trials of long-acting beta2-agonists, or LABAs, in children and adults.

In this brief presentation, I will be

covering background material consisting of some of the key highlights in the recent literature on LABA safety. I will then cover issues that we consider to be important in designing a large LABA safety study. And, finally, I will conclude with a summary of key issues.

So I'll start, as I said, with some pertinent background from the literature and previous advisory committee briefings.

The classic Serevent Nationwide Surveillance Study, or SNS, and Salmeterol Multicenter Asthma Research Trials, or SMART studies, which Dr. Chowdhury mentioned in his talk, showed a three to fourfold increase in risk of serious asthma outcomes in patients receiving LABAs compared to those receiving placebo, with or without other asthma therapy.

Key unanswered questions after these large safety studies include the following. One is whether the occurrence of severe asthma outcomes are increased in patients receiving LABAs in combination with inhaled corticosteroids, or ICS, compared with patients receiving ICS alone.

Another is whether the occurrence of asthma-related hospitalizations are increased in patients receiving LABAs in combination with ICS compared with patients receiving ICS alone.

An FDA meta-analysis was conducted in preparation for the 2008 LABA advisory committee meeting that Dr. Chowdhury mentioned. There was, in this briefing package, found to be a significant trend towards the risk difference of asthma-related hospitalizations being higher at younger ages in individuals receiving LABAs compared to individuals not receiving LABAs.

This slide shows those data in a forest plot. I think this may have been the forest plot that Dr. Chowdhury had been referring to in his discussion. The FDA meta-analysis of approximately 110 trials with approximately 60,000 patients of all ages, half receiving LABA and the other half not receiving LABA, showed a marked age effect in the endpoint of asthma composite index, which was mostly driven, as stated, by hospitalizations for asthma.

The risk difference shown here is

essentially the attributable risk and was measured by the incidence of adverse event in the group that received LABA minus the incidence of adverse event in the comparison group. Overall, combining data for all the LABAs, the youngest patients showed the highest risk and this risk decreased with increasing age.

Again, by way of background, I wanted to remind you of a recent and relevant meta-analysis of 215 studies with approximately 107,000 patients by Weatherall, et al. Parenthetically, many of these patients were from the SMART and SNS studies.

However, in a subgroup analysis comparing LABA plus ICS with ICS alone in 55 studies, they found an increased risk of asthma-related hospitalizations in patients receiving LABA plus ICS compared to ICS alone. And highlighted in the third line of this table, you will see the significantly elevated odds ratio for risk of asthma-related hospitalizations in patients receiving salmeterol plus ICS compared to ICS alone.

Finally, by way of background, I also wanted to mention another recently published relevant meta-

analysis that concluded that long-acting beta-agonists increased the risk for asthma-related intubations and deaths, even when used in a controlled fashion with concomitant inhaled corticosteroids.

This is a busy slide. These are essentially data from Dr. Salpeter's recent meta-analysis published in the American Journal of Medicine. At the top of the slide are data in a red box, which will not be the focus of my comments. I would like to focus your attention on subgroup 2 below, which compared LABA and concomitant inhaled corticosteroid use with inhaled corticosteroid use.

The black line down the middle of the slide indicates risk neutrality and boxes or diamonds to the right of the line favor the control treatment, while those to the left of the line favor the beta-agonist, which, in case number 2, includes inhaled corticosteroids, as well.

There were seven trials considered in this subgroup 2. Note that six of the seven datasets used only one event that was observed in the treatment arm and none in the control arm. Therefore, all the

trials together favored the control and the Peto odds ratio was 3.65, with confidence intervals of 1.39 to 9.55.

There are, undoubtedly, limitations of this study. How were the studies to include in the meta-analysis chosen? Are there alternative methodologies for this process? The meta-analysis necessarily relies on studies that include only one adverse event in the treated group. However, it seems important to be mindful of these results in our discussion of a large safety trial comparing LABA plus ICS use and ICS use alone.

With this background on some of the key studies informing our thinking on study design, I will now move on to discuss study design considerations in conducting a large safety trial for LABAs.

Given the considerations mentioned in the background section, our assessment of the most relevant objective is to assess safety of long-acting beta2-agonist combination products with ICS, that is, Advair or Symbicort, compared to ICS alone, fluticasone or budesonide, in adults and children.

The safety of LABAs alone were tested previously in SNS and SMART trials.

Given our current gaps in safety information related to LABA plus ICS products, we feel that there are two hypotheses that would be important to try to address.

The first is LABA plus ICS use in moderate to severe asthmatics is associated with a greater rate of asthma deaths and intubations than use of ICS alone, and the outcome of interest here, of course, is asthma-related deaths and intubations.

The second hypothesis is LABA plus ICS use in moderate to severe asthmatics is associated with a greater rate of asthma-related hospitalizations than use of ICS alone, and the outcome of interest here, of course, is asthma-related hospitalizations.

So hypothesis number 1 is clinically most important to us, but may require a prohibitive sample size, whereas hypothesis number 2 may also be clinically important, given the data that I showed you from Weatherall, et al, and more feasible. It should be noted, however, that many previous studies with

this hypothesis, and mostly meta-analyses, have had negative results.

Given these hypotheses, relevant arms to the trials would be, first, LABA plus ICS as one agent; and, second, ICS as a single agent. Note that dosing of the ICS in either adults or pediatric trials is a point for advisory committee discussion, as there are many clinical and statistical issues to complicate this choice.

Four separate trials may obtain the appropriate power and the most significant sub-populations. These four trials would include two pediatric and two adult trials, each of the two trials testing the same hypothesis in either Advair or Symbicort.

Here, I would like to mention that consideration should be given to the definition of pediatrics being less than 18 years of age versus less than 12 years of age.

It is not immediately clear which definition would be better from the perspective of allowing the adolescent group to have appropriate powering.

However, we can say that the large studies -- here, I'm referring to SMART and SNS -- done in this area have not been powered specifically to adequately assess adolescent safety.

Note that Symbicort is indicated for children over 11 years of age, so that there would not only be a pediatric Symbicort trial, if pediatrics were defined as those less than 18 years of age. And sample size calculations for such trials as the ones outlined here will be presented by Dr. Neustifter from CDER's Office of Biometrics, but the assumptions that would be used in these calculations are described in this and other slides in my talk.

So all trials would be double-blinded and rescue albuterol would be allowed in all arms of the trial. And our recommendation is to limit the exposure period to LABAs to 3 months, and this recommendation is for several reasons. First, this would be consistent with current labeling, to expose individuals for the shortest period of time to LABAs.

Second, the risks associated with LABAs are not time-dependent, and this was shown in Dr.

Levenson's meta-analysis from the 2008 advisory committee meeting.

Therefore, if the duration of the trial were determined only by likelihood of observing events, the trial would be as long as possible. However, if the duration were determined by clinical recommendations from the label, the time of the trial would be as short as possible. In this case, we're recommending 3 months.

So a non-inferiority study design is appropriate in this instance and it's, obviously, important to decide on an appropriate level of risk to exclude. And studies should include efficacy endpoints to obtain risk-benefit assessment.

The efficacy endpoints should include meaningful health benefits, such as with such indicators as days of school missed, days of work missed, asthma exacerbation, and asthma-related catastrophic events in the groups that receive drug compared to control.

So I'll end by summarizing the key issues raised in this presentation regarding proposed trials

of LABA safety by giving you the following observations.

First, in order to properly power for both adults and pediatric studies, we recommend separate adult and pediatric trials, each properly powered. Second, it is an important point of discussion what is the appropriate level of risk to exclude in these trials.

Third, due to sample size considerations, which will be discussed in detail later, the endpoint of death and intubation related to asthma would not be a feasible endpoint to consider on its own, though, clearly, this would be the most clinically relevant endpoint.

Fourth, the endpoint of asthma-related hospitalization would be feasible and worthwhile, given the background information I showed earlier in the talk, for both adults and children.

Fifth, we should consider a 3-month observation period for the reasons laid out earlier in the talk. Sixth, a point that will need to be deliberated at the advisory committee is the dose of

ICS in pediatric and adult comparator arms.

Finally, given the recent meta-analysis results from Salpeter, et al, consideration should be given to whether we are at equipoise with respect to the safety of LABA plus ICS compared to ICS alone. It seems that the answer to this depends almost entirely on how much weight one assigns to Dr. Salpeter's meta-analysis.

On the one hand, it could be argued that the choice of studies to consider in the meta-analysis was flawed and that if more or different studies were concluded, the conclusion might be different.

On the other hand, the fact that, using any methodology, the results of the odds ratio of close to 4 could be produced may give one pause about conducting a large trial or more than one large trial with exactly those arms.

My colleague from OSE, Dr. Mosholder, will be giving you his interpretation of this and other points shortly.

I'd like to thank those that assisted in this presentation.

DR. SWENSON: Thank you, Dr. McMahon. And now, Dr. Andrew Mosholder from the FDA, in the Office of Epidemiology, will present further perspectives.

DR. MOSHOLDER: Thank you very much. And what I'm going to do here is just very briefly, in about 10 minutes, present some additional perspectives that we think are relevant for the discussion in the next two days. And this presentation is the work of my OSE colleague, Dr. David Graham, and myself and it's worth noting that these are our views and not necessarily those of the FDA or of our Office of Surveillance and Epidemiology.

So with that said, just to start, a recap of the OSE review for the December 2008 advisory committee. And the team recommended at that time or concluded at that time, first, LABA-containing products increase the risk of asthma deaths and intubation in adults and should be assumed to do so in pediatric age group. And, also, the products increase the risk of serious asthma events, deaths, intubations, and hospitalizations in all age groups.

The review team at that time recommended,

first, that the asthma indication for all LABA products be withdrawn for pediatric patients and, also, that the indication for the single-ingredient products, without concomitant steroid, should be withdrawn for adults, as well.

Some considerations relevant to this, first of all, a study to establish whether LABA added to ICS increases deaths, intubation, or hospitalization would be unethical, and I'll have more to say about that. Secondly, and you've heard some discussion of this already, but the ideal characteristics of such studies, if they were to be performed, would be the following -- separate studies for pediatric and adult age groups; separate studies for the two LABA compounds of interest.

The endpoint, ideally, would be asthma death or intubation as the most important and, as we've heard from Dr. McMahon, to be consistent with the new labeling, which emphasizes use for a short a period of time as possible, short-term studies would be ideal, say, on the order of 3 months.

Then, finally, because of the nature of this

study, we would argue that the power should be set higher than traditional, say, at 95 percent, and let me explain a little more about that.

I won't read the text of this, but just the premise is if a trial is to be conducted and finds no difference between two treatments on a safety outcome and then that will be taken as evidence that the treatment under study is safe, then in order to be confident in the result, the argument is you need a higher than standard level of power.

An 80 percent power to find a difference wouldn't give you enough confidence in a null result. So that's why we're arguing that the power should be set higher than traditional at 95 percent.

These are some sample size estimates. And I don't want to anticipate Dr. Neustifter's presentation too much, but I'll just say what we're trying to do here is just show how the sample size would need to be enlarged, first, by increasing the power, but more importantly, by changing the length of the study to 3 months.

What we have here, first, these background

rates are from the December 2008 meta-analysis by Dr. Levenson, from those datasets, and then you see the outcomes broken down here. Obviously, death and intubation, under any assumptions, are going to be prohibitively large sample sizes.

But we're showing here that when you decrease the length of the trial to 3 months, you actually wind up substantially increasing the needed sample size.

So what does this imply for feasibility? Well, recall that SMART was prematurely terminated due to the inability to recruit. The planned enrollment was 60,000 and the actual enrollment after 6 years, when the trial was stopped, was not even 27,000.

So the likelihood of enrolling these very large sample sizes for adults is going to be low and even lower for pediatric patients.

Next, I just want to take a moment or two to comment on the composite outcome. And you've heard some discussion of this already this morning, but basically, the argument here is the composite outcome of deaths, intubations, and hospitalizations may

actually give a misleading result, and let me show you why that's a concern.

These are data from the two large safety trials with salmeterol that you've heard about already, of course, SMART and SNS. And what we have here, these are the relative risks for asthma deaths, the finding from SMART, 4.3, and, from SNS, 3.0, although with a P value of 0.1 rather than standard 0.05.

But then if you look at hospitalizations, you see that for SNS, they were only slightly increased, say, 20 percent with salmeterol versus placebo and then, actually, in SNS, salmeterol was not observed to increase the asthma hospitalization rate at all.

Then the next point is that in a composite, we don't have a composite for SNS, but for SMART, a composite outcome is going to be largely made up of asthma hospitalization events, because they're far more common.

So the argument, if SMART or SNS had been designed to look at asthma hospitalizations, there

really wouldn't have been much of a risk found, and that's why the concern is that that outcome might give a misleadingly reassuring result.

This just summarizes what I just said, that the composite is dominated by hospitalizations and that can be a poor indicator of the directionality of what we care more about, which is intubations and deaths.

Finally, I want to take a few minutes to talk about therapeutic equipoise, and, again, Dr. McMahon has introduced this topic. I'll elaborate. But basically, as I think everyone's familiar with, equipoise is necessary for ethical legitimacy of randomization in a trial, and there are many definitions. Freedman described it as equivalent evidence for alternative hypotheses about the treatments being studied.

Now, taking the case of LABA without an inhaled corticosteroid, I think we would have consensus that equipoise is no longer present. And this is a quote from an editorial about SNS and SMART trials. "In view of the results of the two studies,

the existence of Salmeterol-related excess mortality has to be assumed with near certainty."

In fact, some authors with the Cochrane Review Group actually put statistics on that, combined odds ratio for the two studies close to 4, with a P value of .007. So not much uncertainty about that risk.

So the question now is, are we at equipoise for the treatment condition of LABA plus ICS versus ICS, and, again, as Dr. McMahon mentioned, these two publications, both published in the past few weeks, I should add, a finding in the case of Salpeter, an odds ratio for asthma intubation and deaths of 3.7, with a P value out to .008; and then the Weatherall paper, finding an elevated relative risk for asthma hospitalization.

It's of interest to note, once again, we're seeing a greater -- just comparing the two papers, a greater magnitude of risk for the death and intubation than the hospitalization.

So the question becomes, is there equivalent evidence for reduction of these asthma risks with

LABAs plus ICS. Now, this is, again, the forest plot from the Salpeter paper. I'll just take a moment to make a couple of points here.

But, basically, the premise is with all of the point estimates lining up against the LABA arms in these trials, can we really say that the patients in this group and this group would be considered to be at equal risk for these intubation or deaths.

In this set of trials -- well, the first one is actually a pooled set of trials and the others are single trials. There's a total of 14 events with the beta-agonists and three with the corticosteroids. These were intubations and these were 11 intubations and 3 asthma deaths, and, as we've said, the odds ratio of about 3.7.

Now, all of these trials require that the patient be on inhaled corticosteroid or, in one case, they could have been on an oral corticosteroid. But a subgroup analysis described in the paper, where all the patients received ICS in assigned study treatment showed that the finding was still present, this time with an odds ratio of 8.2, statistically significant.

Then, finally, I'll mention that as an appendix to the paper, there is a reconciliation of these events and a description of them. And just parenthetically, for unclear reasons, three of the events, including the pediatric deaths in this trial, a 13-year-old boy, were reported in other published meta-analyses, but were not part of the datasets FDA received for the December 2008 advisory committee.

So going on, this is, again, a slide you've seen already, but this shows the age trend and the risk difference. That's the excess number of events attributable to the treatment by age group. We see there's a strong age trend, as has been already noticed.

So the point here being that unless you're prepared to accept that concomitant ICS will move these back to a null finding, the interpretation would be that the pediatric age group would actually be bearing the highest burden of excess harmful events from a trial of this nature.

So just to summarize, first of all, the proposed composite asthma outcome may provide

misleading results, for the reasons I mentioned; and, then, secondly, the conduct of a LABA plus ICS versus ICS safety trial appears, at this time, to be unethical.

Instead of at equipoise, there's growing evidence of increased risk. The purpose of the trial would, therefore, be to establish harm with greater certainty.

The risks are probably going to be greatest in the pediatric age group, where the subjects can't give consent themselves and one could argue the ethical burden is greater to protect. Then, finally, initiating a study where there's limited chance of successful completion is also not ethical.

So with that, I'll stop and turn it over to the next speaker. Thank you.

DR. SWENSON: So our next speaker is Dr. Benjamin Neustifter, a mathematical statistician in the FDA.

DR. NEUSTIFTER: Good morning. My name is Dr. Ben Neustifter and I'm the primary statistician from the FDA on this project, with Acting Director

Mark Levenson of Biometrics Division VII as the secondary statistician.

The purpose of this presentation is to provide some estimated sample sizes that would be required for a randomized clinical trial to test the safety of long-acting beta-agonists, or LABAs, as combined with inhaled corticosteroids. These estimates are based on input from both the Office of New Drugs and the Office of Surveillance and Epidemiology and cover a range of power and non-inferiority options to assist the committee in making the recommendations.

The Office of Biostatistics believes that the framework that I will describe is the most appropriate for the present study design and sample size considerations. This framework differs from that in the previous presentation, although it has the same objectives, chiefly, to explicitly demonstrate safety.

First, we will discuss the sample size estimates based on the proposed study designs and assumptions and then we will give a brief overview of why sample size estimates may vary from calculation to

calculation, and quickly touch on some of the reasons that the estimates given in the sponsor's briefings differ from those given in this presentation.

The main portion of this presentation, however, will discuss the assumptions that go into a sample size estimate and the particular choices made by the FDA in our calculations and will provide tables of estimated sample sizes for varying study assumptions.

First, we need to establish some definitions and notation in order to discuss the statistical issues present in the proposed study. The goal of the study is to test if, as stated in the Division of Pulmonary and Allergy Products' memorandum, quote, "the addition of LABAs to ICS in patients with moderate to severe asthma does not increase the risk of serious asthma outcomes."

This wording makes it clear that the proposed study should be a non-inferiority trial; that is, one that attempts to show that a treatment of LABA plus ICS is not significantly less safe than a treatment of ICS alone. Subjects will be assigned to

receive LABA plus ICS or ICS alone during this trial.

For the purposes of this presentation, we'll be using pL to represent the true probability of severe asthma events for treatment of LAVA plus ICS during the study and pC to represent that probability for the control treatment of ICS alone.

Delta and delta-star represent the non-inferiority margin. This is the cutoff point that determines what is a clinically significant difference in rates between the two treatments.

The goal of the non-inferiority trial will be to determine if a treatment of LABA plus ICS has an associated event rate that is greater than that of the ICS alone treatment that's greater by this margin.

Finally, we would like to note that there are several ways of testing for non-inferiority. Two of the most common are using the risk difference or the relative risk or risk ratio. The difference between these will be discussed on the next slide.

It's important to note that while the two methods have similar results, the sample size estimates will differ slightly between the two. While

the FDA suggests the use of the risk difference in the study, we will discuss the relative risk briefly, as well, since some of the sponsors used this statistic in their briefings.

The hypotheses for a non-inferiority trial are slightly different depending upon whether the relative risk or the risk difference is the statistic being used.

The risk difference is the absolute difference in probability of severe asthma event between the two treatments. For example, we might observe that one treatment has a risk of event 1 in 10,000 greater than the other treatment.

For this statistic, the null and alternative hypotheses are about the differences between pL and pC. Note that for a non-inferiority trial, the null -- that is, the hypothesis we assume to be true, unless the evidence proves otherwise -- is that the LABA plus ICS treatment does have a probability of event greater than that of the ICS alone treatment, where we define a significant difference to be one that is greater than this non-inferiority margin delta.

Thus, we begin with the hypothesis that the treatment of LABA plus ICS is inferior to an ICS alone treatment, from a safety standpoint, meaning that it's related to a significantly higher risk of serious asthma events, and it is up to the data from the study to disprove this notion.

The relative risk is about the relative difference in probability of an event between the two treatments. For example, we might find that one treatment has a probability of events that is 10 percent greater than the other treatment. So rather than focusing on the absolute difference in probability between the two, we examine the proportion of risk increase in the alternative treatment comparative control.

Thus, the hypotheses, instead of testing the difference, test the ratio of the two event rates. Again, we assume that the LABA plus ICS treatment does have a significantly greater probability of a severe asthma event, so that the ratio of treatments' event rates is greater than the non-inferiority margin, delta-star.

Note that this delta star is most likely a different number than the risk difference non-inferiority margin, delta, but there is an equivalency between the two. It's possible to convert one to the other.

In order to estimate the sample size necessary for a study, there are several parameters that we need to assume or estimate values for. Alpha is the rate of Type I error or in this particular study, it's the probability of the data determining that a LABA plus ICS treatment is not inferior to the ICS treatment with respect to severe asthma events when, in fact, it is inferior.

Again, note that when we say not inferior, we mean that the LABA plus ICS treatment appears to be as safe as the ICS alone treatment with regards to serious asthma events, at least within some small margin. And inferior indicates that the LABA plus ICS treatment has a significantly higher risk of serious asthma events.

One-minus-beta is the desired power. It's our chances of the data correctly showing that the

LABA plus ICS treatment is not inferior to the ICS treatment. Delta or delta-star is the non-inferiority margin, which we discussed on previous slides. Finally, pL and pC, as we discussed before, are the background rates of events for the two treatments.

All the sample size calculations in this presentation are made under the assumption that these two rates are actually the same as some background rate p. This is a standard assumption for power and sample size calculations.

We'll discuss this point further later, but we'd like to preface this discussion by stating that changes in any of the many assumptions that go into a sample size calculation, it can change the estimates one obtains. These effects will be particularly noteworthy when we discuss how the sponsor's briefing documents compare to the FDA's with regard to these assumptions.

This means that changing alpha, the probability of Type I error, or the power or the non-inferiority margin or using a different estimate of the rate of event occurrence or adding assumptions

about dropout or regional heterogeneity to your calculations can all change the resulting sample size estimate.

In particular, changes in the assumed rate of event occurrence can be caused by several factors, including changing the study length, changing the endpoint for your study, say, from death to a composite endpoint of hospitalization and death and intubation, or coming up with your estimate of this rate from a different study.

Finally, note that the test chosen, whether it's risk difference or relative risk or some other statistic, will also affect the sample size estimate. This presentation will be providing estimates for the risk difference. The relative risk estimates are provided in some backup slides that, unfortunately, weren't included in the packets, but are available in the slideshow. And the risk difference estimates in the case of the study universally tend to be lower than the relative risk estimates.

For the FDA's sample size calculations, we used the following assumptions. We assumed alpha, the

maximum allowable chance of Type I error, is 0.025. This is the standard choice for non-inferiority trials. And we assumed either 80 percent or 90 percent power, both of which are also standard for sample size calculations.

For the risk difference, we assumed that the non-inferiority margin is some proportion of the true background rate, either .2, .3, or .5 of the background rate p. Likewise, for the relative risk, we're assuming the non-inferiority margin to be an increase of 20 percent, 30 percent, or 50 percent above the background rate.

You can see the risk difference and relative risk non-inferiority margins are functionally equivalent to each other. They both correspond to 20, 30, or 50 percent increases in the risk, and that goes back to that equivalency between the two that we discussed before.

For either non-inferiority margin, the input of the advisory committee is needed to determine a margin that balances clinical significance with study feasibility.

Creating assumptions about p, the true background probability of asthma events, is the most difficult portion of sample size calculations, as it depends upon many factors. For example, we need to decide upon the definition of an event, whether it could be asthma-related deaths, which are quite rare, but are the strongest concern, or it could be the composite endpoint, defined by the 2008 advisory committee of asthma-related deaths, intubations, and hospitalizations, or some other definition.

An endpoint of death is likely of the greatest clinical concern, since a difference of death rates between treatments could pose a great safety risk. In order to estimate the background death probability, we looked at the meta-analysis performed by the FDA for the 2008 advisory committee on LABA safety.

In the trials that involved a LABA plus ICS treatment versus an ICS alone treatment, 1 subject out of 15,192 died across trials. This gives an approximate death rate of 0.66 per 10,000 subjects.

The median length of treatment in those

studies was 91 days or approximately one-quarter of a year. Thus, assuming that asthma-related deaths have a constant rate over time, we multiply 0.66 times 4 to get 2.64 estimated asthma-related deaths per 10,000 subjects per year or an approximate annual rate of 0.03 percent.

Clearly, asthma-related death is a very rare event and this leads to prohibitively large sample sizes for randomized clinical trials attempting to study this. The Office of Surveillance and Epidemiology is suggesting that a 3-month trial should be considered.

This presentation won't consider this length of trial for an endpoint of death, since the sample sizes for even a year-long trial are already infeasible.

It's important to note that the sample size estimates for a death endpoint are incredibly rough. The estimate of a death rate is based upon a single event from the 2008 meta-analysis. So these should be considered to be ballpark figures for sample size.

They're mostly intended to show the

infeasibility of a randomized clinical trial of LABA plus ICS, plus ICS alone, with a death-only endpoint.

An alternative choice of endpoint is the composite endpoint defined for the 2008 meta-analysis. This endpoint is defined by asthma-related deaths, intubations and hospitalizations. Clearly, since asthma-related deaths and intubations are quite rare, this composite endpoint will be largely driven by asthma-related hospitalizations. Whether this is appropriate or not is a clinical issue that will not be addressed by this presentation.

Assuming, again, that asthma-related events, now defined by this composite endpoint, are constant over time, the 2008 meta-analysis gives approximate rates of .375 percent for a 3-month study, .75 percent for a 6-month study, or 1.5 percent for a year-long study.

We include these rates and we also bracket them by more extreme rates of .25 percent and 2 percent, and then we finally include the rates .5 percent and 1 percent and some middle ground in order to provide better coverage of the possible values of

p.

As some justification for these estimates of the background rate, if we look at the American Lung Association's January 2009 report on asthma, we can see that in 2006, the year with the most recent data available, about 1.94 percent of all Americans with asthma had an asthma-related hospitalization. This rate is within our bracketing values of 2 percent, though it is on the high end.

We note that this background rate is probably higher than that of the clinical trial background rate, since the ALA data covers all American asthmatics, including those with no medical care or those who are misusing or not receiving treatment. So a clinical trial background rate is likely going to be lower than this 1.94 percent.

By these estimations, we are giving these approximate background rates. For a year-long study, specifically, we have the approximate background rates of .01, .015, or .02.

Finally, we must also consider the background rate for a pediatric population. In this

context, we're following the Department of Pulmonary and Allergy Products' definition of pediatric as meaning 4 to 11 years old.

From the data from the 2008 meta-analysis, we get an estimate of .35 percent of subjects age 4 to 11 having an asthma event in a quarter-year, where here we defined an asthma event as an asthma-related hospitalization.

Again, assuming that these asthma-related hospitalizations are constant rate over time, that means .7 percent of subjects should have an event over a 6-month study or 1.4 percent over a year-long study. These are the estimates for p that we'll be using for the pediatric population.

For alternative estimates, we can look at the National Center for Health Statistics' 2006 report on childhood asthma, which gives an annual rate of asthma of 3.19 percent for asthmatics aged 0 to 17. Note that this is not the same range of ages as the pediatric population of interest, but it was the only one available from the National Center for Health Statistics' study.

We can infer from this the quarter-year and half-year probabilities of events, as well, of .8 percent and 1.6 percent, assuming a constant rate over time. Note that these rates are quite a bit larger than the ones given by the 2008 meta-analysis and are from a more broad population.

They are likely too high for the clinical population being considered and are included only as an upper bound on the pediatric rates. The sample size estimates gained from these values should not be considered as reliable without further research.

Thus, we have an estimate of .014 for p for a 12-month trial, and these are the rates for a 3 and 6-months trial. And then we have these upper bracketing rates from the National Center for Health Statistics that should be taken with caution.

Before giving the sample size estimates under these assumptions, I'd like to clarify a few points. First, these sample size estimates assume that the study is a two-arm trial of LABA plus ICS versus ICS alone treatments, with equal sample sizes assigned to each arm.

If a three-arm trial is desired, these estimates on the next couple slides should be multiplied by 1.5 to increase them by 50 percent, ignoring the multiplicity that may be present in such a design.

Second, these estimates assume that there are no dropout subjects during this trial. If one wants to assume, say, a 10 percent dropout rate, these estimates should be multiplied by 1.1 to increase them accordingly.

Third, these estimates also assume no regional heterogeneity. If these trials are multicenter, especially if the centers are located in different countries, there may be significant differences in asthma rates and variants between sites, which would increase the necessary sample size. This should be examined and accounted for when designing the final study.

To fit the time constraints, this presentation will only give the estimates for 12-month trials in the main body. Sample size estimates for the 3 and 6-month trials are included in the appendix

of backup slides.

Similarly, only estimates based on the risk difference are being included in the main body of this presentation, since the FDA feels that this statistic is more appropriate and results in smaller sample sizes. Relative risk sample size estimates are also included in the appendix of backup slides.

Finally, to make these tables easier to read, the sample sizes provided are rounded to the nearest two significant digits and, thus, might be slightly smaller or larger than the actual numbers given by the formulas.

Here, we have the sample size estimates for a 12-month trial on adults, with an endpoint of death. You can see here the estimated background rate of .0003, as discussed earlier.

This next column lists the three different non-inferiority margins. The number on the left is the absolute difference in risk and the number in the parentheses on the right is the relative increase in risk over the background rate.

This illustrates the earlier comments given

regarding the equivalence that exists between the risk difference and relative risk non-inferiority margins.

So, for example, if we wanted to rule out an absolute risk difference of .00015, which is 50 percent of the background rate, for an 80 percent power study, we would require a total sample size of 420,000 subjects, and, for a 90 percent power study, we'd need a total sample size of 560,000 subjects.

Note that in all these slides, the sample size estimate is for the total sample size, not the sample size for each arm. So in this example, this 420,000 subject estimate means that each arm should be assigned 210,000, half of this number. As you can see, the sample sizes for a death endpoint trial are prohibitively large, even for a year-long treatment.

This slide contains the total sample sizes estimates for a 12-month treatment trial in adults, with the composite endpoint of asthma-related death, intubation, and hospitalization. For example, if we think the background rate estimate of .015 is reasonable and we want to rule out an absolute risk increase of .0045, which is 30 percent of the

background rate, then an 80 percent power trial would require 23,000 subjects total and a 90 percent power trial would require 31,000 subjects total.

Recall that these estimates do not account for dropout or regional heterogeneity. You can use different background rates or other choices and non-inferiority margins similarly to help make decisions regarding study feasibility.

Finally, this slide contains the sample size estimates for the pediatric population for a year-long treatment study. Recall that the starred background rate and the associated estimates come from the data from the National Center for Health Statistics, which is from an overly broad population and are likely too high. They're included only to give an extreme minimum for sample sizes.

As an example, if we take the meta-analysis background rate of .016 and an absolute risk difference non-inferiority margin of .0048, which is 30 percent of the background rate, an 80 percent power study would require 21,000 subjects total or a 90 percent power would require 29,000 subjects total.

In the second portion of this presentation, we'll discuss why sample size estimates may vary from organization to organization and, specifically, compare and contrast some of the major assumptions of the three sponsors' briefings from the FDA's sample size assumptions.

To briefly recap, there are several assumptions that, if changed, can result in a different sample size estimate for a study. If a higher power is desired, a larger sample size is necessary. If a smaller non-inferiority margin is desired in order to detect smaller differences in treatments, a larger sample size would also be necessary.

Changes in the background probability of events p can quite drastically change the sample size. The estimated background probability might be changed due to treatment length, choice of endpoint, or estimating p from a different study. Additionally, adding dropout assumptions or regional heterogeneity assumptions will cause the sample size estimate to be larger.

Finally, the method used for testing the hypothesis, whether it's relative risk or risk difference or some other method, will also change the estimated sample size.

Now, we will take each of the sponsors' briefings, in turn, and highlight some of the larger differences in assumptions between their estimates and the FDA's to provide the committee with some insight into the varying sample size estimates obtained by each organization.

I'm going to do these next couple of slides out of order from the way they're printed, because I notice that they're actually backwards from the way the sponsors are presenting and I want to present them in the same order the sponsors are presenting, to help kind of eliminate confusion.

So I'm actually going to start with GlaxoSmithKline. So GlaxoSmithKline used a power of 90 percent when calculating their sample sizes for randomized clinical trials. However, they only used an 80 percent power when discussing the sample sizes for an observational trial.

They used the relative risk rather than the risk difference, which will cause some differences in sample size estimates. Their non-inferiority margins of 1.25 and 1.4 are not quite the same, but similar to the FDA's non-inferiority margins.

The main difference between GSK's estimates and the FDA's for sample sizes are the estimated background rates. You can see that GSK uses estimates of .58 and .61 percent, which are lower than the FDA's estimates of 1, 1.5, and 2 percent. Both of these estimates were obtained from studies within the FDA meta-analysis from 2008, but the GSK only used those studies which concerned Advair, which is GSK's product.

These studies comprised the majority of subjects in the LABA plus ICS versus ICS alone treatments in the meta-analysis. The main reason GSK's rates differ from the FDA's estimates has to do with the treatment length of the studies involved.

Recall that earlier, when I was discussing the FDA's estimates of the background rate, we obtained an estimate of the background rate from the

meta-analysis and said that the median treatment length was 91 days or a quarter of a year. Thus, we multiplied the 3-month rate by 4 to get the year-long rate estimates of 1, 1.5, and 2 percent.

Since there were some studies of much longer length, the majority of studies involved in the meta-analysis, the distribution of the treatment length is heavily skewed, causing the mean treatment length and the median length to be quite different from each other.

Specifically, the mean treatment length from the meta-analysis was almost 6 months long, about 180 days or half a year. GSK used this as the indicator of average treatment length. So when they got their estimates, they only multiplied them by 2 to get the annual rate rather than multiply them by 4 to get the annual rate, as the FDA did. That explains why their estimates are approximately half of the FDA's.

Finally, GSK is also assuming a 10 percent dropout rate, while the FDA doesn't have such an assumption, which is also going to cause GSK's sample sizes to be estimated to be larger than the FDA's.

AstraZeneca assumed 90 percent power, which is the higher of the two powers the FDA estimated, and they are also using the relative risk rather than the risk difference.

AstraZeneca provides several non-inferiority margins that are quite a bit larger than the FDA's. They used 30 percent and 50 percent increase, as the FDA did, but then they also have non-inferiority margins of 2, 2.5, 3, 4 and 5, which correspond to a cutoff of clinical significance at somewhere from 100 percent to 400 percent risk increase.

Such margins are associated with smaller sample sizes, but this may be at the cost of clinical meaningfulness.

The estimated background rates from AstraZeneca are 1 and 1.5 percent, which are similar to those estimated by the FDA. And like the FDA, the AstraZeneca had no dropout assumptions.

Therefore, the main differences between the AstraZeneca and the FDA sample size assumptions will be due to the use of the relative risk and largely to these different non-inferiority margins.

Finally, Novartis gives 80 percent power, which is the lower of the two FDA powers provided, and they are using the risk difference, similar to the FDA. Their non-inferiority margins are absolute rather than being proportional to the rates, the way the FDA's are, and they're similar, but a bit lower than the FDA's, in general.

Notice that Novartis estimates the true background rate to be .3 or .6 percent, which is lower than the FDA's estimates. This is going to result in high sample sizes, in general.

The reason that their rates are different is that they didn't estimate them from the 2008 meta-analysis data. Rather, they estimated them from two other studies. Similarly, their pediatric rates are different, though in the same ballpark, largely, as the FDA's estimates for pediatrics and, again, this is due to the fact that they estimated those rates from different studies.

Neither Novartis nor the FDA used a dropout assumption. Thus, the main differences between the sample size estimates will be with the different

background rates used by Novartis and associated, the smaller non-inferiority margins used by Novartis.

So this concludes the FDA's presentation on the statistical issues present in the design of a study testing the non-inferiority of a LABA plus ICS treatment against an ICS alone treatment with regard to the occurrence of severe asthma events.

At this point, we would like to summarize the questions of statistical importance that should be considered by the advisory committee. First, the study design, obviously, has a large effect on sample size and power. In particular, the number of arms of the study should make a large impact on the study sample size.

Second, the decision of what to use for the study endpoint affects the background rate of events and, thus, affects the sample size. A broader endpoint, such as the FDA's composite endpoint from 2008, will allow for a smaller sample size to obtain results, but may be of less clinical significance. Rare endpoints, such as death or intubation, may be more meaningful, but can result in much larger sample

sizes.

Third, the duration of the treatment, likewise, affects the background rates and, thus, the sample size. A longer treatment length may increase the number of subjects who have events, lowering the necessary sample size, but may increase dropout if extended too far.

Fourth, the advisory committee should consider what the power of the study should be. A lower power leads to smaller sample sizes, but means that the study is more likely to result in a possibly erroneous decision regarding the lack of safety in LABAs.

Finally, the advisory committee must decide upon a non-inferiority margin that balances the feasibility of the study with clinical meaningfulness. A larger non-inferiority margin lowers the sample size necessary, but makes small increases in risk harder to detect.

As a final example from the tables given, if the committee, for example, decided on a two-arm study with a year-long treatment in adults using 80 percent

power and the FDA's composite endpoint of death, intubation, and hospitalization, and set the non-inferiority margin at 30 percent of the event rate, and we're assuming the background rate here is .015, so that's a relative increase of 30 percent, the study would require approximately 23,000 subjects total, ignoring any dropout or regional heterogeneity.

We hope that the information in this presentation and the associated briefing helped the advisory committee in making these decisions.

DR. SWENSON: Thank you very much. Our schedule, at this point, would have called us to have a brief question session, but the presentations have gone on just a little bit longer, not too badly.

But I thought that for sake of maintaining our schedule, that, at this point, we'll take a 15-minute break and then we'll resume with the rest of the FDA presentation. So we'll meet back here at 10:20.

(Whereupon, a recess was taken.)

DR. SWENSON: We'll resume the FDA's presentation, and Grace Chai, from the Division of

Epidemiology, will now present.

DR. CHAI: Good morning. I am Grace Chai, a drug utilization analyst in the Office of Surveillance and Epidemiology. Today, I will be presenting the outpatient utilization patterns of long-acting beta2-adrenergic agonists, otherwise known as LABAs, in the U.S. for years 2002 to 2009.

The following is an outline of my presentation. Today, I will describe the extent of LABA-containing product use in the U.S. outpatient retail setting from year 2002 to 2009. The products listed below were included in this analysis.

The drug use reviews presented in this analysis were not limited to the asthma indication, unless otherwise noted. Sales data were obtained from IMS Health to determine the distribution of LABA products. In year 2009, the majority of LABA-containing products were distributed to outpatient pharmacy settings, with 55 percent of the LABA market distributed to retail pharmacy settings; 30 percent and 15 percent were distributed to mail order and non-retail pharmacy settings.

This analysis focuses on the outpatient retail pharmacy utilization data. Mail order data and inpatient data were not included in this analysis.

The following data sources were used to analyze outpatient utilization patterns. SDI's VONA and TPT are national level projected prescription and patient-centric tracking services. Data are obtained from a sample of 59,000 pharmacies throughout the U.S., accounting for nearly all retail pharmacies and nearly half of all retail prescriptions dispensed nationwide.

SCI's PDDA is a monthly survey that monitors disease states and physician-intended prescribing habits on the national level. The database contains data from 3,200 physician specialists in the panel that report on all patient activity during one typical workday per month, which is then projected nationally.

Next, I will be presenting the results of the analysis. This graph represents the inhaled corticosteroid and LABA-containing product market in all age populations by the number of prescriptions dispensed from the outpatient retail pharmacies from

year 2002 to 2009. Dispensed prescriptions for ICS products were included to show LABA-containing product use in comparison to ICS product use.

The total number of LABA prescriptions increased from 16 million in year 2002 to 22 million in 2009, as denoted by the gray column. However, the growth in the number of prescriptions dispensed slowed in year 2005.

Of the LABA-containing product market in year 2009, combination LABA products accounted for 62 percent of all LABA and ICS products. Prescriptions for salmeterol/fluticasone increased from 10 million prescriptions in year 2002 to 18 million prescriptions in year 2009. However, prescriptions for a single-agent LABA product salmeterol decreased from 5 million in year 2002 to 500,000 prescriptions in year 2009.

Of the ICS-containing products, fluticasone was the top single-agent ICS prescription dispensed. However, prescriptions for fluticasone decreased from 7 million in 2002 to 5 million prescriptions in year 2009.

This graph represents the ICS and LABA-

containing product market in the pediatric population, defined as patients age 0 to 11 years old, by the number of prescriptions dispensed from outpatient retail pharmacies year 2002 to 2009.

LABA use has decreased in the pediatric population since year 2005. In total, LABA prescriptions dispensed to the pediatric population decreased from 1 million prescriptions in year 2002, which represents approximately 25 percent of the pediatric ICS and LABA market, to 870,000 prescriptions in 2009, which represents approximately 16 percent of the pediatric LABA/ICS market.

Of the LABA-containing products, the majority were dispensed as salmeterol/fluticasone, though use has been decreasing since year 2005. Salmeterol prescriptions dispensed to the pediatric populations decreased from 200,000 prescriptions in year 2002, which represents 5 percent of the ICS/LABA market, to 2,000 prescriptions, which represents 0.04 percent of the ICS and LABA market in year 2009.

In contrast to the findings of the total population of all ages, the majority of pediatric use

were for single-agent ICS products. In year 2009, 2 million prescriptions were dispensed for budesonide and 1.6 were dispensed for fluticasone, compared to 700,000 dispensed for salmeterol/fluticasone.

DR. PLATTS-MILLS: I apologize for interrupting. Is this prescriptions for 1 year or is it each month is a separate prescription?

DR. CHAI: Year. These are year 2002, 2003, 2004.

DR. PLATTS-MILL: No. But you say that it's 12 -- a number. Is that each month counted as a separate prescription --

DR. CHAI: No.

DR. PLATTS-MILLS: -- or a prescription that says for 1 year?

DR. CHAI: It's the total number of prescriptions dispensed in that entire year.

DR. PLATTS-MILLS: But if it's dispensed once a month, that's 12 --

DR. CHAI: So 12 prescriptions dispensed once a month will equal 12 for that year.

DR. PLATTS-MILLS: So 12 million

prescriptions means 1 million patients.

DR. CHAI: Not necessarily. The patient slides are coming up.

This table shows the total number of dispensed prescriptions for LABAs by product strength for patients age 0 to 11 years old and patients age 12 years and older in the U.S. outpatient retail market.

For example, if the Advair Diskus products, the most commonly dispensed strength was for Advair 100 micrograms in the 0 to 11 pediatric population and Advair 250 micrograms was the most popular Advair strength in the 12-plus years population.

This is the patient graph I was referring to. The following are graphs of the total number of unique patients by patient age receiving a LABA prescription from U.S. outpatient retail pharmacies from years 2002 to 2009. The graph on the left shows the total number of unique patients of all ages and the graph on the right shows the total number of pediatric patients 0 to 11 years old. Please note the difference in the scale of the Y-axis.

There was a total of 6 million patients, 6.2

million patients of all ages prescribed LABAs in year 2009; 5.2 percent of the total number of patients were pediatric patients, approximately 300,000 patients age 0 to 11 years old prescribed the LABA in 2009.

Although there was a general increase in the number of LABA patients of all ages, there was a decrease in pediatric patients since year 2005. The patient trends reflected dispensed prescription trends.

This graph represents the proportion of LABA drug use mentions with the associated diagnosis for asthma, COPD, or other diagnosis, as reported by office-based physicians from year 2002 to 2009.

The top diagnoses for all ages were for asthma-related diagnoses. COPD was the second highest diagnosis, although this was primarily in the adult population. Formoterol was associated with the highest proportion of diagnoses for COPD.

This analysis was representative of national outpatient retail pharmacy usage patterns. However, mail order and inpatient use were not captured in this analysis. Only 55 percent of the total LABA sales

distribution was analyzed. The data presented may be an underestimation of the total U.S. use of LABA-containing products.

OSE conducted further analysis regarding single-agent LABA salmeterol use. This analysis was conducted to characterize the patterns of salmeterol concurrent medication and medications that preceded salmeterol use. Unlike the previous slides, this analysis only includes patients with a diagnosis of asthma.

IMS' PharMetrics Health Plan claims database, a longitudinal, patient-centric claims database, was utilized for this study. The study population consisted of 7,608 asthma patients of all ages with an incident use of salmeterol for study period of year 2005 to 2007.

An incident use is defined as a patient with a prescription for salmeterol who did not have a salmeterol exposure in the previous 6 months.

Concurrency was defined as having at least 1 day of overlapping therapy between salmeterol and another asthma medication. The results of the

concurrency analysis found the majority of patients on salmeterol were on concurrent ICS/SABA therapy, short-acting beta-agonist.

Seventy-seven percent of the study patients used salmeterol with a short-acting beta-agonist and 60 percent used salmeterol with an ICS. However, the proportion of days of concurrent therapy for ICS and SABAs was very low.

The proportions were calculated based on the number of days of concurrent therapy divided by the total number of days on salmeterol and then the median was taken of that calculation.

The 0.16 means that 16 percent of the total time on the salmeterol therapy, there was an overlap of concurrent therapy. It was also found that 6 percent of all patients on salmeterol did not have any overlapping therapy days with any other asthma medication during the salmeterol therapy episode.

Prior RX use was defined as prescriptions for an asthma medication 90 days prior to a salmeterol prescription. The results of the prior RX use analysis found that the majority of patients on

salmeterol received a prior asthma prescription.

It was found that 67 percent of the study patients had a SABA RX filled prior to salmeterol, 53 percent had an ICS prescription filled prior to salmeterol, and 33 percent had a leukotriene modifier prescription filled prior to salmeterol.

However, 20 percent of salmeterol episodes were not preceded by any other asthma medication in the 90 days prior to the salmeterol use. These findings suggest current labeling is not entirely followed.

In summary, the use of LABA-containing products in all age populations increased over the examined time period, but growth stabilized since year 2005. However, use in the pediatric population, defined as age 0 to 11 years old, of LABA-containing products is decreasing. Pediatric use accounted for 4 percent of the total LABA use in year 2009.

Salmeterol/fluticasone was the most commonly prescribed LABA-containing product. Single-agent LABA product use is decreasing, especially in the pediatric population, and single-agent ICS products were used

more frequently over LABAs in the pediatric population.

The analysis of salmeterol concurrent and prior use suggests that current labeling is not entirely followed in practice.

Thank you.

DR. SWENSON: Thank you, Dr. Chai. And, Dr. Chowdhury, you have some closing remarks here before we go into the question session.

DR. CHOWDHURY: Thank you, Chair. My closing remark actually was to go into the questions and introduce the questions for the committee to hear and for everybody to be aware of what are the questions that we are posing here for discussion. And these questions are merely, again, as a starting point for discussions.

We have a total of seven and what I will do here is not to read the questions in detail, but just to briefly go over the concept and the outlines to put everybody on the same page with these questions.

The first question is regarding the study endpoint. As you have heard in our presentations, we

are proposing a composite which includes asthma-related death, hospitalization, and intubation. And we have got three points for you to consider as you discuss.

The first is adequacy of this endpoint. And the second is what level of risk for LABAs would be considered acceptable to rule out; that is, what would be an acceptable upper bound of the 95 percent confidence interval. We'd also like to hear alternate endpoints that one could consider for this question.

The second question is similar to the previous one, but this one is specifically for pediatric patients. And for the pediatric patient, the endpoint that we are putting out for discussion is just asthma-related hospitalization and the points that we are bringing up for discussion are essentially parallel to the question number one, which is the adequacy of this endpoint, the level of risk, and are there alternate endpoints that one should consider.

The third and fourth question goes a bit more into design elements that we touched on earlier and this question is on one aspect of the design,

which is given the hypothesis to be tested, we want you to discuss the advantage versus disadvantage of a study where corticosteroids are given in the real world situation, meaning the corticosteroid doses can be adjusted as opposed to a situation where the corticosteroid dose remained fixed.

Recall, in my presentation, I had one slide where I showed a couple of options with fixed dose versus variable dose corticosteroid. This question gets to that and we want you to give input on this aspect both for adult and adolescent studies and, also, for the pediatric studies.

This, again, is a follow-up to the previous question, again, on the design element, and, here, then going with the inhaled corticosteroid dose. We want some discussions whether the dose should remain the same as the dose in the combination product or whether the ICS dose should be higher.

Recall the treatment guidelines, where a combination product is given when necessary and when it is being stepped up. The choices are for a patient to be stepped up to the next high dose of

corticosteroid versus adding a dose of a low-acting beta-agonist.

So this question gets into this discussion whether the design of the trial that we are considering, should the dose of steroid be the same or be higher.

Question five is, again, on the design element and here, the issue is the length of the clinical trial both for adults and pediatrics. And the three lengths that you have heard being presented here, the first is 12 months, going down is 6 months, and the other one is 3 months.

The next question is on the timeframe and we want some discussions around a reasonable timeframe for the study to complete.

The other question is regarding the African-American patients, who, as we discussed earlier, bears a high burden of the disease, has more mortality and more morbidity. And if you recall the SMART study, the signal was stronger in that sub-population.

So we want you to discuss the challenges in obtaining meaningful information for this subgroup,

which, obviously, is relevant and important.

That's all the comments I wanted to make. Thank you.

DR. SWENSON: Okay. Thank you, Dr. Chowdhury. We do now have time to open up for questions specifically to the FDA members with respect to their talks, and I believe Dr. Krishnan has the first question.

DR. KRISHNAN: Thank you, Mr. Chairman. I would like some clarification from the FDA on what is the deliverable that you're asking for the committee to think over.

It seems to me, from the agenda and much of the talks presented today, that you're asking questions about the design of a randomized clinical trial and some input in the development of such trial. Yet, one of the speakers from the FDA seems to suggest that we're no longer in equipoise and we already have sufficient data to say that such a trial would potentially be unethical.

So I guess the question I'm asking is, are we here to deliberate about the need for additional

data from a trial or are we here to give some advice on the design of a clinical trial, having already made the decision that a trial is needed?

DR. ROSEBRAUGH: Well, I think it's kind of both. So we certainly want design trial advice, but if, after hearing that presentation, you think we're no longer at equipoise, we would want to hear about that, as well.

DR. SWENSON: Dr. Brittain?

DR. BRITTAIN: Yes. I have a couple questions for the statistician. I wanted, first, sort of a nitty-gritty question about the rates. With the composite endpoint, if I understand correctly, with 10,000 patients in a year, you'd expect 150 composite endpoint events and I think three of those you thought would be doubts.

So what would be the breakdown in terms of intubation? You didn't mention that.

DR. NEUSTIFTER: That's a very good question. Actually, looking at the 2008 meta-analysis data that we based these rates on, the only intubation was also the death. So, actually, if we were going to

estimate based solely on the meta-analysis data, which is what we did, the death and intubation rates are exactly the same.

DR. BRITTAIN: But they were the same person.

DR. NEUSTIFTER: Yes.

DR. BRITTAIN: So it would really only be one.

DR. NEUSTIFTER: A death, right. I mean, they were intubated before they died.

DR. BRITTAIN: Okay. And the other question I had was it sounds like the idea is for multiple studies to be done with the different drugs, if I'm understanding correctly.

Would there be a role for a meta-analysis so that you could get a more precise estimate of some of these rare events?

DR. NEUSTIFTER: I don't see a statistical reason why we couldn't pool the data from the studies to do a meta-analysis, but I don't have any advice on what the impact on the study design for those individual studies would be then.

DR. BRITTAIN: I didn't know what the regulatory perspective was on that.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: I just want to expand this discussion that was raised directly by Dr. McMahon and by Drs. Mosholder and Graham, but implicitly by Dr. Chowdhury, which is the question of equipoise and the related question of the ability to recruit patients to a trial, given at least an arguable lack of equipoise.

So it's not just limited to the Weatherall and the Salpeter recent, last month or two, meta-analysis. But it's also affected enormously by the relatively new FDA position that's been taken, which is basically to tilt away from the use of LABAs.

Both Dr. Chowdhury and Dr. Jenkins, in the press briefing a couple weeks ago, announced a new policy, which was gone over by Dr. Chowdhury this morning, use LABAs for the shortest duration of time possible or, conversely, they should only be used in people who have really had an adequate trial, and I think they meant not just low dose, but mid dose of steroids, as well.

So how would you design an informed consent sheet that incorporated by the Salpeter results, the Weatherall results, and the FDA's current position? Because if you were a patient, aware that you should be on corticosteroids only, unless you couldn't be controlled with them, A, and where, if you have already been controlled on a combination of corticosteroid and LABA, you should get off the LABA as soon as possible.

Even a 3-month trial, which is what it sounds like, at least the going more likely length of trial, if one is done, would get a number of people off of a current recommendation made by the FDA.

So my question to everyone from the FDA is how do you reconcile both the two meta-analyses, the recent ones, and the current FDA position, which are all arguing against equipoise, as in equivalent evidence on both sides.

If there's equivalent evidence, aside from the two meta-analyses, the FDA would not be making the recommendation they're making now.

DR. JENKINS: I would say, in many ways,

you're asking the question we're asking you to answer, as the members of the committee today.

DR. WOLFE: John, that's a copout.

DR. JENKINS: No. Let me finish, Sid.

DR. WOLFE: Because you thought --

DR. JENKINS: I let you finish. You can let me finish. The issue of how we have crafted what we recommend in the labeling for clinical use of the long-acting beta-agonist can be considered basically an excess of caution -- don't use these products unless you really need them.

But we recognize that there will be a significant number of patients with asthma who will need to be on these products and who will need to be on these products chronically. So that factors in, as Dr. Chowdhury said, about what population of patients you might choose to enroll into the study.

I think it's up to the committee to offer your advice about issues related to how definitive you think the findings are, about the risk, when used in combination with inhaled corticosteroids. Much of the data that we see presented, outside the most recent

meta-analyses, are from the older studies, where concomitant corticosteroids were not used as often as they are today and as they would be used in the current study.

You have to think about what you think of the Salpeter meta-analysis and the other new data in reaching that conclusion. We believe, and I think many others have stated the position, that this is a question that needs to be answered through further controlled clinical trials.

We're asking you for help in designing trials that answer the question, that are feasible, and, also, you'll have to give us your advice about the ethics of those trials.

DR. WOLFE: A quick follow-up question, which is, simply, in the discussion, in the very excellent briefing material that was handed out, one of the considerations would be that entrance in the trial would require that the person is already stabilized, which makes a lot of sense in terms of avoiding regression at the mean and so forth.

So if the person is already stabilized on

whatever they're on, there's just a further detail on the dilemma, because the advice from the FDA is once you're stabilized, you should go off the LABA. The advice in designing the trial is you should only use people that are stabilized.

DR. JENKINS: But, again, I think our point in the labeling recommendations is about how to guide clinical practice. There is still an unanswered question, in many people's minds, about whether the risk is mitigated by use of the corticosteroid concomitantly, and that's something that we believe could be studied in a clinical trial, where you've got very careful controls over the monitoring of the patients.

You've got a data safety monitoring committee that's monitoring the safety of the trial as it emerges over time. You have escape criteria. So we don't believe that the labeling itself define exactly the study that you have to do in order to try to get a further answer to this question.

So, again, these are the questions we're asking the committee to grapple with. It's exactly

why we're here today. We recognize that these are very complicated and difficult questions, and we essentially have one more chance to get this right.

We need to do studies that do the best we possibly can to get an answer to this question, unless you tell us that you don't think the question can be answered by any ethical or feasible or practical study. And then you'll have to give us advice about where that leaves us with these still unanswered questions.

We knew that this was going to be a very controversial topic and that's why we're here today and tomorrow to get your advice and, also, some degree of community buy-in, because we're going to require these studies to be done by the companies and we're asking your advice on how to require those and what the most feasible and practicable studies might be.

As I said, this is probably our last best chance to get an answer to these questions and it would be nice to avoid the inevitable second-guessing down the road -- well, if you had asked for this or if you had asked for that, you would have gotten a better

answer.

We're asking you, prospectively, to help us design the best studies we can to get the best answer we can.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: So I have a couple of questions. The first question is that I wasn't aware of the Salpeter article. So the absolute risk rates in the Salpeter article are very, very different than what's been presented as the absolute risk.

They're the order of, for the non-treated group, about 1 in 1,000 patients, and that would probably even -- I don't know how long those studies were, but that would probably be -- if it's 6-month duration, that would be like 1 in 500.

So I'd like to know, is the design of that study such that those absolute risks aren't relevant?

DR. FLEMING: David, you have to go to the discussion of the article, because -- David Schoenfeld, Tom Fleming here -- you're looking at their analysis, the odds ratio analysis, which, correctly, is only using the studies with at least one

event. But you get a very biased representation of the absolute.

DR. SCHOENFELD: I see. Okay. That's what I wanted to know.

DR. FLEMING: In the discussion, to get absolute, they add in all the zero studies to be able to give you the context for absolute.

DR. SCHOENFELD: I see. Okay. So the absolute risk is much, much less, because that picture was only in the studies with one event. So the relative risk is correct, but the absolute risk is wrong.

DR. MOSHOLDER: Yes, that's precisely right. And if you look in the discussion of the article, page 5, I guess it is, there's some estimates of the absolute risk.

I did a little arithmetic. I got one excess risk per 1,400 patient years of treatment as a ballpark. That's for intubation or death.

DR. FLEMING: That's correct.

DR. MOSHOLDER: You can compare that to the SMART and the SNS trials, where the estimates were

about 1 in 750 person years of treatment for an excess death. So one supposition is that the ICS may be sort of reducing the overall rate, but the imbalance attributable to the LABA is still observed.

DR. SCHOENFELD: But the excess is 1 in 1,400, which means --

DR. MOSHOLDER: Person years.

DR. SCHOENFELD: That's about a three or four-fold relative risk. So the absolute risk is still -- is it still higher than the numbers that have been used for the sample size?

DR. FLEMING: The absolute risk is 6.4 per 10,000. In SMART, it was 41 per 10,000. The excess risk is 7.1 per 10,000 in Salpeter. It's 21.1 per 10,000 in SMART.

DR. SCHOENFELD: So it's 2 per 1,000. The baseline risk in these studies -- in Salpeter is what? Maybe repeat it, because it went by too fast for all of us.

DR. FLEMING: So in Salpeter, it's 6.4 per 10,000.

DR. SCHOENFELD: 6.4.

DR. FLEMING: Asthma-related death/intubation, it's 6.4 per 10,000, from their discussion materials.

DR. SCHOENFELD: Okay.

DR. FLEMING: In contrast, it's 41 per 10,000 in SMART, sevenfold higher.

DR. SCHOENFELD: In SMART, okay, the underlying risk, the baseline risk. So it's something in the order of 6 per 10,000. And the figures used for the sample size considerations were how much per 10,000?

DR. FLEMING: Three.

DR. SCHOENFELD: Most of your sample size for death and intubations.

DR. NEUSTIFTER: Ben Neustifter. This 3 per 10,000 was the estimated rate we got from the 2008 meta-analysis.

DR. SCHOENFELD: I see. So it's about twofold difference.

DR. NEUSTIFTER: Yes.

DR. SCHOENFELD: Okay. So that sort of clears up some of the confusions about those huge

rates in the Salpeter analysis that are very troublesome. It's because they only considered the patients who were -- the studies that had at least one event and that sort of ups the rates. And the relative risk is still right, but what they got was about 6 per 10,000, which is about twice what was used before.

What I'm curious about is anybody -- the way I look at this is that most of the deltas seem to be very small, to me; that is, it would seem to me that people are willing to accept and physicians are willing to accept some risk when they give a patient a drug, if the symptomatic benefit is great enough.

So I was wondering if there's any discussion -- it's a little bit hard, because the symptomatic benefit is hard to measure, also. It sounded to me like there was kind of -- people don't necessarily know they're being helped when they're given a combination product. They may be being helped by each product.

So the comparison of the combination to the single agent kind of measures the benefit. And

looking at that, it seemed like it's translated this into a number needed to treat. It was about 1 to 5 or something of that order. So it's very hard to discuss the benefit.

But I guess the real issue that we need a discussion of -- and if anybody has anything that they've sort of studied on this -- in terms of absolute risk, what is an acceptable absolute risk to a patient of a therapy that may improve their symptoms; maybe in 1 out of 5, dramatically, and then the rest, a smaller amount.

DR. SWENSON: We have time for one more question, because I don't want to get off track here.

DR. SCHOENFELD: But if someone from the FDA has studied that issue, I'd be interested in their answer.

DR. SWENSON: Do we have anybody from the FDA to answer that question? Okay. Well, it's certainly a subject for much more thought and we do have considerable time to ponder these in the next hours and tomorrow.

We have time for one more question, and I'm

trying to do this as fairly as possible, in order, and our next question will be from Dr. Cnaan.

DR. CNAAN: Yes, a brief question. There was an underlying assumption of a constant exposure rate in considering to do 3 months, 6 months, 12 months. Can anybody at the FDA provide any evidence for supporting, whatever, of whether the rate is really constant?

DR. NEUSTIFTER: Ben Neustifter. And we looked at the 2008 meta-analysis data and we looked at Kaplan-Meier plots of the event rates and it appeared that it was -- looked like it was a largely constant rate.

So, yes, we looked at the Kaplan-Meier plots and it appeared to be a constant rate over time for the composite endpoint.

DR. SWENSON: We'll now have to move on to stay on schedule. We'll have a sponsor presentation from GlaxoSmithKline. Dr. Knobil?

DR. KNOBIL: Thank you, Dr. Swenson. Good morning. My name is Katherine Knobil and I am Vice President of Clinical Development in the Respiratory

Medicines Development Center at GlaxoSmithKline. I'm also a pulmonologist, with experience in the treatment of patients with asthma and COPD, as well as other respiratory diseases.

On behalf of GlaxoSmithKline, I would like to thank the agency and the advisory committees for this opportunity to participate in the discussion about study designs for serious asthma-related outcomes when long-acting beta-agonists are added to inhaled corticosteroids, as in Advair.

Our presentation will be divided into several sections that will address different aspects relevant to the question before the committee today. In a moment, I will discuss study design considerations to examine Advair in rare asthma-related events, and then I will invite Dr. Carlos Camargo to present GSK's proposed observational study. I will then return to summarize our study recommendations.

We recognize that the FDA has proposed studying a composite endpoint in a randomized controlled trial. Our study proposals provide an

alternative approach to the questions before the committee today. GSK will be recommending two studies.

The primary recommendation, a case control study, would directly address the question of whether the addition of a long-acting beta-agonist, or LABA, to inhaled corticosteroids increases the risk of asthma-related death.

The second study, a randomized control trial, would examine the relationship between Advair and FP on the outcome of asthma exacerbations requiring oral corticosteroids.

The presentation today will provide our rationale for these recommendations. We believe that these two studies will complement each other in answering the questions that have been raised on the safety of long-acting beta-agonists.

Shown here is the overview of my presentation, which covers a broad range of topics, all related to the question under discussion today. Rather than read the outline to you, I will return to the outline throughout the presentation; and, in the

interest of time, I'll jump right in.

It's important to recognize that the prevalence and burden of asthma continue to rise. This diagram, from the current asthma treatment guidelines, commonly referred to as EPR-3, and sponsored by NHLBI and NIH, shows that asthma is complex and characterized by an underlying inflammatory process.

This results in an interaction between airflow obstruction and airway hyperresponsiveness, leading to variable and recurring symptoms. Bronchoconstriction is the dominant physiological event leading to clinical symptoms and as the disease becomes more persistent and inflammation more progressive, airway edema and potentially structural changes contribute to airflow limitation.

The goal of asthma management is to control current impairments, such as shortness of breath and cough, and nighttime awakenings due to dyspnea, and to continually maintain control, while also preventing future risk, such as unpredictable, serious asthma exacerbations.

Anti-inflammatory treatment with an inhaled corticosteroid can control some of these processes for many patients, but treatment with an inhaled corticosteroid alone is often incomplete.

The science-based expert panel responsible for EPR-3, after systematically reviewing all published literature, chose adding a LABA to low dose ICS as a preferred treatment for adolescents and adult patients and a recommended treatment in children not controlled on low dose ICS alone.

GSK acknowledges that for some, a question remains if salmeterol, when used with concurrent inhaled corticosteroids, increases the risk of rare asthma-related events. Based on the results of the Salmeterol Multicenter Asthma Research Trial, or SMART, we believe that the pertinent question is, does the addition of a LABA to an ICS, as in Advair, increase the risk of asthma-related death.

You have already heard that the FDA has proposed a composite endpoint of asthma-related death, intubations, and hospitalizations and while these are all important endpoints, the agency also recognizes in

their briefing document that the primary question relates to the most serious -- asthma-related death. We will, however, discuss all of these endpoints during the course of the presentation.

If salmeterol was strongly associated with an increase in asthma-related death, asthma mortality rates would likely reflect this trend. This slide shows that the U.S. mortality rate from asthma, shown in red, has steadily declined from 1996 to 2007, falling from a peak of over 5,600 deaths in 1996 to approximately 3,300 in 2007.

The increasing use of inhaled corticosteroids, shown in blue, is believed to have contributed to this decline, as inhaled corticosteroids are the only class of asthma medications to be associated with a reduction in asthma mortality.

It is noteworthy that the continual decline in asthma mortality has also occurred during the period when long-acting beta-agonist use has increased for both asthma and COPD, as shown here in yellow.

Advair became available in 2001 and is

reflected in the curve by the inflection in both the blue and yellow lines. Today, nearly all long-acting beta-agonist use for the treatment of asthma is with concurrent inhaled corticosteroids through fixed combination inhalers, such as Advair.

The use of Serevent has evolved to reflect appropriate use, as recommended by guidelines. When Serevent was introduced in 1994, the role of inflammation in the pathophysiology of asthma was not widely appreciated and bronchodilators were often prescribed alone. As a result, in the period between 1994 and 1996, about one-third of Serevent was dispensed with no other controller medication at all.

This figure shows the percentage of all treated patients with asthma who were dispensed Serevent from 2003 to 2009 and illustrates how prescribing practices for Serevent have evolved based on guideline recommendations and educational efforts.

If we focus on 2009, we can see that the use of Serevent without a controller is less than 1 percent overall and is one-tenth of 1 percent for children age 4 to 11, and, also, for adolescents age

12 to 17.

However, it is important to remember that Serevent also has an exercise-induced bronchospasm indication and for those patients without persistent asthma, Serevent does remain an appropriate treatment option.

Finally, to put today's use of salmeterol for asthma into context, salmeterol is dispensed alone as Serevent less than 1 percent of the time. The remaining salmeterol use is in combination with FP in Advair. However, the debate concerning salmeterol centers on data obtained when Serevent was not routinely used with inhaled corticosteroids.

The results from SMART provide the rationale for the primary research question. These data and some of the following data have been presented and discussed during previous advisory committee meetings.

As you will recall, SMART studied Serevent and not Advair. The study was initiated in 1996 and compared Serevent to placebo when added to usual asthma care. Over 26,000 patients were enrolled in the study.

The results for the total population will be shown in yellow. Results for patients reporting ICS use at baseline will be shown in blue, and those not reporting ICS at baseline will be shown in white.

In SMART, fewer than half of the patients reported using ICS at baseline. There was a low number of events. For the total population, there was an increase in asthma-related death and asthma-related death and intubations combined. Asthma-related hospitalizations were also slightly increased, although this result was not statistically significant.

When we look at the group of patients in blue who reported using ICS at baseline, there was no significant increase in serious asthma outcomes. And for your reference, here are the data for patients not reporting ICS use at baseline.

Overall, there was a reduction in the rate of serious asthma outcomes when patients reported that they were taking ICS at baseline. This result is reassuring, but since the use of ICS was not required during the study, one cannot draw firm conclusions

about the protective effects of inhaled corticosteroids in this case.

Next, I will review the data with Advair when the use of ICS with salmeterol was assured. Data from randomized controlled trials with Advair provide more evidence that long-acting beta-agonists do not increase the rate of serious asthma-related events when the use of inhaled corticosteroids is assured.

These results from the GSK meta-analysis of Advair studies were presented as part of the 2008 joint advisory committee. In the overall population, there were no asthma-related deaths or intubations in over 22,000 patients receiving Advair or ICS.

Earlier, you heard Drs. McMahon and Mosholder refer to the Salpeter meta-analysis. You'll also recall that Dr. McMahon referred to potential limitations in the choice of the studies included in that meta-analysis.

I'd like to pause here to clarify something very important. None of the data from the studies of Advair were included, as there were no deaths and no intubations in over 22,000 patients. Therefore, these

data were not taken into account in the Salpeter meta-analysis.

The data in the pediatric population are a subset of the overall population. In over 2,400 children, there were no deaths and no intubations. Further, there was no increased risk in asthma-related hospitalizations in children.

Finally, another subset of the overall population that we examined was exacerbations requiring oral corticosteroids from all U.S. studies comparing Advair to FP. As you can see, for this endpoint, there was a clear benefit of Advair over FP.

A separate meta-analysis was conducted of observational cohort studies to assess the benefit of Advair compared with inhaled corticosteroids in reducing emergency department visits and hospitalizations in clinical practice. The analysis in adults included nearly 83,000 patients, with 59,000 on Advair.

For asthma-related emergency department visits, there was a 16 percent decrease for Advair treatment compared with inhaled corticosteroids, which

was statistically significant. There was a 15 percent decrease in the risk of asthma-related hospitalizations for Advair compared with ICS, which was also significant.

In pediatrics, a similar meta-analysis was performed that included over 43,000 children and adolescents less than 17 years of age, with over 16,000 receiving Advair.

It is important to point out that asthma-related hospitalizations in children and adolescents is uncommon. In fact, for every nine emergency department visits that occurred in the study, there was only one hospitalization.

As a result of the low frequency of asthma-related hospitalizations, only the combined endpoint of asthma-related emergency department visits or hospitalizations could be analyzed.

When Advair was compared with inhaled corticosteroids, there was a significant decrease in the number of pediatric patients with an emergency department visit or hospitalization. When Advair was compared to ICS plus montelukast, there was a 54

percent decrease in the number of patients with an emergency department visit or hospitalization, again, showing that Advair was significantly more effective than the combination of ICS plus montelukast in reducing this outcome in children.

Therefore, the evidence from clinical practice in adults and children demonstrates that the use of Advair decreases the risk of serious asthma-related events, including hospitalizations and emergency department visits.

The data that I've just shown you were generated in the context of stepping up with a LABA versus adding another controller. The following studies show the implications of stepping down from Advair.

The objective of these two identical studies, initiated in 2001, was to evaluate whether patients who were stable on Advair 150 could maintain asthma stability when continued on the same dose of Advair, shown in blue, or stepping down to FP, shown in yellow, salmeterol in green, or montelukast in red.

Advair treatment was significantly better

than all of the other treatments, including FP, in lung function, daytime and nighttime symptoms, and rescue albuterol use. There were higher numbers of exacerbations in all of the groups when compared with Advair.

More importantly, as shown by these two studies, asthma stability deteriorated more in the treatment groups that discontinued Advair, which led to a significant increase in withdrawals due to worsening asthma.

These studies support that treatment of underlying bronchoconstriction, as well as inflammation, is required to maintain optimal asthma control.

In short-term studies, serious outcomes are rarely seen. The data I'm about to show you demonstrates the effect of discontinuing Advair on more serious asthma outcomes.

Results of this retrospective cohort study using health insurance claims data showed that inpatients previously maintained on moderate or high doses of Advair, those that stepped down to a lower

dose of Advair compared to those who stepped down to the same dose of FP experienced better asthma control, as measured by significantly lower albuterol use, a significantly lower risk of receiving a systemic corticosteroid, a significantly lower risk of having an asthma-related emergency department visit, and, while a rare event, there were fewer asthma-related hospitalizations, zero with Advair and three with FP.

Therefore, patients who discontinued Advair by stepping down to an equipotent dose of FP had an increased risk of serious asthma events compared with those who stepped down to a lower strength of Advair.

Based on the extensive database for Advair, including the data that I've just reviewed, the 2008 joint advisory committee returned a unanimous vote supporting the positive benefit-to-risk profile in adults. The vote was positive, but not unanimous, for the younger age groups, largely due to the fact that there were fewer efficacy studies in pediatrics to support the benefit side of the equation.

As a result, the committee requested additional data for Advair in children to better

characterize the efficacy profile. Since then, new studies with Advair have been completed.

The NIH CARE Network study, known as BADGER, which was described by Dr. Robert Lemanske at the 2008 joint advisory committee meeting, has been completed and the results have been published in the New England Journal of Medicine just last week.

BADGER was a three-period crossover study to determine the best step-up care in children aged 6 to 17 years of age who remained symptomatic on ICS alone. After an 8-week run-in period, patients who remained symptomatic on FP 100 twice daily were randomized to Advair 150, FP 100 plus montelukast or FP 250.

The primary outcome was a composite of asthma exacerbations, asthma control days, and FEV-1. Overall, Advair 150 twice daily was most likely to produce the best response. Advair was 1.6 times more likely than FP plus montelukast to be the best step-up therapy, and 1.7 times more likely to be the best step-up treatment than FP 250.

In addition, there were several factors that predicted improved responses. Higher scores on the

asthma control test and children's asthma control test predicted a better response to Advair, as did white race. Black patients were least likely to have a best response to adding a leukotriene receptor antagonist.

There was one hospitalization in each treatment group. Treatment failures were defined as a hospitalization or the need for more than one prednisone burst. There were 4 treatment failures with Advair, 9 with FP 250, and 12 with FP plus montelukast. Total prednisone bursts followed a similar pattern as treatment failures, with 30, 47, and 43 bursts in each treatment group, respectively.

In addition to BADGER, GSK has also completed three studies with Advair in children aged 4 to 16 years of age. The details of these GSK studies are described in your briefing document.

Overall, the results from these studies showed that Advair was either superior or as effective as doubling the dose of FP, and these studies are complementary to the BADGER results that I just showed you.

Taken together, these new studies address

the request from the 2008 joint advisory committee to demonstrate significant benefits in children and supports the positive benefit-to-risk profile of Advair in children.

As I mentioned earlier, the question for today is what studies could be done to address whether the addition of a LABA to an inhaled corticosteroid increases the risk for asthma-related death.

So what is the best approach for Advair? Asthma-related death is a very rare event and with Advair, we have seen no evidence of an increased risk in asthma-related death or other serious asthma outcomes.

When evaluating efficacy, randomized controlled trials are considered the gold standard. However, when addressing rare safety outcomes, a randomized clinical trial may not be feasible and other scientifically credible study approaches should be considered.

This list illustrates some of the elements that must be considered when designing a clinical trial. The proper balance between each element must

be achieved in order for a study design to be considered scientifically and clinically valid and meet ethical considerations.

Each element is important, but those highlighted here are the ones that have a considerable influence on design considerations on a study with Advair. I will discuss the top two in some detail now and the others will be discussed during the course of the presentation.

The agency has acknowledged that studying the outcome of asthma-related death is not feasible. As an alternative, the agency has proposed that studying a composite endpoint of asthma-related deaths, intubations, or hospitalizations may be feasible.

It should be recognized that the informative value of asthma-related intubations and hospitalizations on asthma-related death is limited. Asthma-related intubations are also very rare and hospitalizations are not informative on the primary outcome of asthma-related death.

An analysis from a representative sample of

U.S. hospitals in 2006 reported over 65,000 asthma-related hospitalizations. Of these, 4 percent resulted in an intubation and only .5 percent of hospitalizations resulted in an asthma-related death.

Therefore, the proposed composite endpoint of asthma-related death, intubation, or hospitalizations would effectively measure only hospitalizations and would not provide conclusive evidence on asthma-related death. Despite this, we evaluated the composite endpoint and sample size estimations and feasibility assessments, which I will discuss in a few minutes.

One could compromise the design of a very large study to make it more feasible, but this would have an impact on the scientific validity and the clinical relevance of the results. For example, the level of risk to exclude could be increased or the power could be decreased in order to reduce the required sample size.

For a safety study, we believe that the level of risk to exclude should be small and clinically relevant, not exceeding 1.25. There is no

guidance for the level of risk to exclude for serious asthma outcomes, but a small risk to exclude is consistent with FDA's guidance for cardiovascular events in patients with diabetes, which recommends that the level of risk to exclude should be 1.3.

I'll take you through a hypothetical example of what happens when you increase the margin of risk to exclude. Based on the data from clinical trials and observational studies, it is likely that the point estimate for a study comparing Advair to ICS would be less than or equal to 1. For this hypothetical example, let's assume that the point estimate is 1, suggesting that there's no differential treatment effect.

A risk to exclude of 1.25 would ensure that a study could demonstrate that Advair was not associated with more than a 25 percent increase in the outcome of interest. However, if the study was designed with a large level of risk to exclude, for example, 2, results from a study could only technically rule out that Advair is not associated with a two-fold or 100 percent increase in excess

risk, even if the point estimate was 1.

As this hypothetical example demonstrates, a study design with a large risk margin would likely produce inconclusive results, which do not allow clear clinical interpretation.

I've discussed the important elements that influence study design. And so the next step is to determine what effect a particular study design would have on the estimated sample size. This slide lists the design assumptions we used in estimating sample sizes for a randomized controlled trial of serious outcomes.

From a clinical perspective, the hypothesis to be tested is that Advair is no worse than FP in the incidence of serious outcome of interest. In other words, this would be a non-inferiority study comparing Advair to FP.

The risk to exclude would be set at 25 percent. The power would be set at 90 percent, and the treatment period would be 12 months to ensure that all patients were exposed to study drug during seasonal at-risk periods.

The overall background rate was determined from the ICS-containing arms of the GSK meta-analysis of 63 trials that included over 22,000 patients, comparing Advair with inhaled corticosteroids. In over 5,000 patient years of exposure, there were no deaths in patients receiving inhaled corticosteroids.

In order to estimate the sample size required, the number of deaths was imputed at 1. Therefore, the normalized background rate is 2 per 10,000 treatment years of exposure.

With these assumptions, the estimated sample size to rule out a 25 percent increase in asthma-related death for Advair as compared with FP is over 4 million patients.

If we increase the risk margin to rule out a 40 percent increase in asthma-related death, approximately 2 million patients would still be required. Therefore, we agree with the agency that such a study is not feasible.

Now, let's look at the sample size estimate for the composite endpoint of asthma-related death or intubation or hospitalizations. As there were no

deaths or intubations in the ICS group in the GSK meta-analysis, the sample size estimate was based only on the number of hospitalizations, which results in a rate of 58 per 10,000 treatment years.

The estimated sample size to rule out a 25 percent increase in the composite endpoint is approximately 154,000 patients. To rule out a 40 percent increase, approximately 68,000 patients would be required.

Further, as you're aware, the FDA has suggested conducting a randomized controlled trial in pediatric patients, evaluating the endpoint of asthma-related hospitalizations. The background rate for asthma-related hospitalizations in children was based upon the GSK meta-analysis and is 120 per 10,000 patient years.

The estimated sample size to rule out a 25 percent increase in asthma-related hospitalizations in children is approximately 73,000 patients. To rule out a 40 percent increase, approximately 32,000 patients would still be required.

So for adults and children, the sample size

becomes smaller when the risk to exclude is increased to 40 percent. But is even this lower number of patients feasible to enroll?

After calculating how many patients are required to study Advair and FP in randomized controlled trials, feasibility assessments were conducted to determine if and when results from the studies could be delivered. We based the feasibility exercise on a flexible study design concept, described in the briefing document.

There are a few assumptions that you should be aware of. Baseline asthma severity should be appropriate for the treatment of Advair and to facilitate enrollment, we would include as broad a population as possible. As a result, patients could receive any strength of Advair or the corresponding equipotent dose of FP. Stratification would ensure that equal numbers of patients receive Advair or FP for each FP dose.

Since the question is whether adding a LABA increases the risk for serious asthma outcomes, allowing the dose of FP to be titrated over the course

of the study for an individual patient would make interpretation of the results difficult.

Therefore, we believe that the FP dose should be equal within a treatment stratum and constant through the course of the study. We made sure that randomized treatment was consistent with asthma treatment guidelines. Therefore, no patients would be stepped down to induce asthma outcomes.

We also based on the feasibility on consultation with investigators and experts experienced in enrolling patients into clinical trials and we assumed that patient recruitment would include at least 20 countries. We also reviewed actual enrollment durations for similar populations from completed GSK studies.

As a result of this exercise, we estimate that we could enroll approximately 4,000 patients per year into such an asthma trial. For comparison, trials in cardiovascular disease have been known to enroll patients more quickly.

Part of the context for this is that in adults, the prevalence of elevated cholesterol, for

example, is approximately 6 times that of moderate to severe asthma and the number of hospitalizations for ischemic cardiac disease is approximately 4 times more common than hospitalizations for asthma.

The differences in disease prevalence and event rates highlight the challenges that we face in enrolling eligible patients into large studies of rare asthma events.

Therefore, based on the sample size estimates that I spoke of earlier, a randomized controlled trial, with a composite endpoint excluding a 25 percent increase in risk, would take approximately 38 years to enroll. If we increase the risk to exclude 40 percent, the enrollment period would require a minimum of 17 years.

This number is consistent with our experience with SMART, which enrolled 26,000 patients over 6 years. However, this enrollment figure does not take into account some very important factors.

A study with the objective to rule out severe asthma events would be challenging for IRB approvals, physician-investigator participation, and

patient-informed consent. There's also the potential for change in the standard of care over time, the impact of large competing safety studies, and how, in our experience with long-term studies, enrollment wanes over time.

The feasibility estimates for a study of hospitalizations in children was based upon our experience from previous trials. In the best case, the estimated enrollment is approximately 1,000 children per year. Therefore, a study of hospitalizations in children would take at least 32 years.

The information that I've just reviewed shows that conducting a randomized control trial with FDA's recommended composite endpoint of asthma-related death, intubation, and hospitalization in adults and adolescents or hospitalizations in children cannot be achieved in a reasonable period of time.

However, GSK can continue to explore what study could be feasibly done comparing Advair with FP. Of all of the outcomes reported in the meta-analysis of randomized controlled trials with salmeterol, the

next most frequent outcome was oral corticosteroid-requiring exacerbations.

While this endpoint does not inform directly on the outcome of asthma-related death, it is a clinically relevant outcome for both patients and physicians.

Based on the data that are available for Advair compared with FP, which includes numerical decreases in single studies and a significant decrease in the meta-analysis, GSK proposes a randomized controlled trial to confirm the benefits seen in these previous studies.

For this study, we assumed a superiority design, with 90 percent power and a 12-month treatment period. The background rate was determined from the ICS arms in GSK studies of exacerbations, and approximately 20 percent of patients experienced an exacerbation requiring an oral corticosteroid.

Events from such a trial would almost exclusively include outpatient outcomes, but would also collect information on death, intubations, hospitalizations, and emergency department visits,

should they occur.

In this scenario, approximately 3,000 patients would be required for an adequately powered study to demonstrate a 25 percent reduction in exacerbations requiring oral corticosteroids. This study could include children, as well, and we would stratify by age. However, an adequately powered study in children aged 4 to 11 could be considered as a separate trial.

Asthma exacerbations are more common in children and, therefore, the background rate determined from the pediatric trials with Advair was slightly higher, at 30 percent.

To conduct an adequately powered randomized controlled trial that demonstrates a 25 percent reduction in exacerbations requiring oral corticosteroids in children, approximately 2,000 patients would be needed. Based on our experience, it takes at least 4 times longer to enroll the same number of children as it does adults. So in the best case, it would take this study in children a minimum of 2 years to enroll.

The assumptions for a randomized controlled trial are based on the current labeling. However, you've just heard about the proposed labeling that has been discussed by the FDA, and the proposed changes will likely have an impact on the ability to do such a trial.

The approved indications for Advair and accepted standards for use directly affect the design, conduct, and feasibility of any clinical trial comparing Advair and ICS. While this advisory committee has not been asked to consider the recent proposed labeling changes for Advair, the impact of such changes are relevant for the discussion today.

Shown on this slide are the four main elements of the proposed changes to the Advair label discussed by FDA during the press conference on February 18th. The first described that LABAs would be contraindicated without the use of an asthma controller medication, such as an inhaled corticosteroid. We agree with this recommendation, and this was consistent with the GSK labeling supplement that we submitted in September of 2008.

The second described that LABAs should only be used long-term in patients whose asthma is not adequately controlled on asthma controller medications. We agree that patients should only be on the medicines required to maintain asthma control. However, adequately controlled asthma will need to be defined.

We also agree with the last bullet that pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product to ensure compliance with both medications.

The third bullet calls for LABAs to be used for the shortest period of time required to achieve asthma control and then discontinued. At first, you may not perceive that this is a major change to the current labeling or treatment guidelines. However, further review of the specific recommendations revealed a significant deviation from asthma treatment guideline recommendations.

On the same day as the press release, FDA provided sponsors with specific labeling changes to

reflect their current thinking. The proposed labeling changes are based on the premise that salmeterol, even in the presence of an inhaled corticosteroid, places patients at increased risk of serious asthma outcomes.

This presumption of risk does not take into account over 10 years of clinical trial data with Advair, which has shown no asthma-related deaths, no intubations, and no increase in hospitalizations in adults or children with Advair.

Specifically, the revised labeling states, "Once asthma control is achieved, discontinue Advair Diskus and maintain patients on an asthma controller medication, such as an inhaled corticosteroid." There is no evidence for the mandate to discontinue Advair after patients have achieved control.

Additionally, a mandate to discontinue is inconsistent with the available data and, as I've just shown you, may result in unintended public health consequences.

The presumption of risk has also led to the loss of the indication for the maintenance treatment of asthma. Therefore, treating patients for a

prolonged period of time would be precluded by the proposed label.

Earlier, I described why a randomized controlled trial to study asthma-related death, intubation, or hospitalization would not be feasible in a reasonable period of time. However, a study of exacerbations requiring oral corticosteroids could be completed, but only if mandated step-down is not required as part of the study design.

The proposed label to discontinue Advair once asthma control is achieved would make even this study very difficult to conduct, for the following reasons: Step-down labeling would limit exposure, which is needed to detect serious outcomes; ethics approval of long-term use is uncertain in the context of the revised label; and, obtaining informed consent from patients is also uncertain, as the benefit has been minimized in the label and in the medication guide.

Due to the inability of a randomized controlled trial to meaningfully inform on the risk of asthma-related death, GSK explored other options

available to study rare events. As a result of this exercise and in collaboration with the Asthma Mortality Working Group assembled by GSK, we recommend an observational study as the most appropriate study design to assess rare, serious asthma-related events.

An observational approach is within the FDA's draft guidance for industry, Post-Marketing Studies and Clinical Trials. This guidance states that if other investigations, for example, an observational study, can adequately address the question of interest, then a randomized controlled trial should not be required.

An observational study is a feasible, scientifically valid option, using a clinically relevant risk to exclude that can directly assess the outcome of asthma-related death and can address whether the addition of a LABA to an ICS increases the risk of asthma-related death; and, importantly, the results would be available in a reasonable period of time.

I would like to introduce Dr. Carlos Camargo, a member of the Asthma Mortality Working

Group that I just mentioned, to describe this proposal. Dr. Camargo is the past President of the American College of Epidemiology, is the past Chair of the AAAAI Asthma Mortality Committee, a member of the NIH Asthma Guidelines Committee, and Associate Professor at Harvard Medical School.

Dr. Camargo?

DR. CAMARGO: Great. Thank you very much, everyone. As you heard, my name is Carlos Camargo and I'm an emergency physician and epidemiologist at Mass General Hospital and Harvard Medical School.

I should disclose, as requested by Dr. Swenson, that I'm receiving a consulting fee and travel expenses from GSK for participating in this FDA meeting. I do not have any other financial relationship with the company. I'm in full compliance with my hospital and Harvard Medical School conflict of interest guidelines.

So from my perspective, as an emergency physician who is focused on the treatment of severe asthma exacerbations and as an epidemiologist who has a strong interest in asthma outcomes, I'm going to

speak to the role of an observational study and a specific study that would evaluate the relationship between the introduction of LABAs, specifically, Advair, and asthma-related mortality.

As members of the committee are well aware, observational studies play a key role in understanding post-marketing safety of medications. U.S. Government agencies have put considerable resources into improving the infrastructure to conduct studies of drug safety using real world observational data in large electronic data systems, and this slide shows two examples.

One is from the FDA, which is the Sentinel Initiative, which aims to create a national, integrated, electronic system for monitoring medical product safety throughout the product's life cycle.

Another very important initiative is from the Agency for Healthcare Research and Quality, and this is the DEcIDE Centers, and the aim there is to develop a research network to conduct population-based studies and safety surveillance. Already, six HMO research network health plans are developing a

prototype, merging electronic medical records and claims data, and informing the development of a larger, multipurpose research network, which includes both private and public partners.

As you can imagine, these efforts are highly relevant to our discussion today and encourage serious consideration of alternatives to randomized trials when the question is a rare event and lengthy patient exposure to the drug of interest is the concern, and that is precisely our situation.

So for the question before us today, I'd like to highlight some of the strengths and limitations of observational studies. Several strengths explain why observational studies are used so often as part of post-marketing safety evaluations and one of the most important is generalizability.

As you can imagine, studying real patients taking their medicines in the way patients do gives it credibility and is informative in a way that patients take the medicine. So I think that's perhaps one of the strongest advantages.

But very closely following that is the idea

that these studies can address rare events, because of the large number of patients and events that can be included. So as a result, observational studies of rare events can achieve adequate statistical power, in contrast to these randomized trial designs that you've just heard discussed by Dr. Knobil.

Especially important to this issue and a safety issue is timeliness. And to be more specific, it would be possible to complete the study, a large and rigorous study of Advair use, that I'm going to present to you today, in about 3 or 4 years.

Now, a limitation of observational research is a potential misclassification of drug use from pharmacy records. But this potential bias is not unique to observational research. RCTs can also have misclassification when patient-reported adherence does not reflect actual use.

But the bigger problem with observational studies is the one that involves this issue of nonrandomized assignment. Clearly, we're watching people and what they do and there is not a random assignment of the medication.

Now, the challenge here is that sicker people will get more medicines and have worse outcomes. It's confounding by severity, confounding by indication, and the false signal that a medication is harmful when it's not. That's the challenge of observational research.

Since 2007, GSK has convened meetings with nine experts on asthma mortality and pharmacoepidemiology from the U.S., the U.K., New Zealand, and you'll find a list of the names in the appendix of the briefing document provided by GSK. These experts met in person and on a series of teleconferences to grapple with this difficult issue of how to study LABAs and asthma mortality.

The objectives of these meetings were to review the relevant data from randomized trials and observational studies; to discuss a wide range of possible study designs and the challenges of the different approaches; and, finally, we sought to develop consensus on how to further evaluate salmeterol safety, and this last activity included a formal feasibility assessment.

Well, the consensus of the Asthma Mortality Working Group was that an observational study design was the most scientifically credible and operationally feasible approach to address this LABA asthma mortality question. And specifically, the working group, in which I participated, recommended a nested case control study, meaning one that is nested in a large cohort of patients with persistent asthma.

Critical to this effort is that the study design must account for that confounding that I referred to earlier, the confounding by indication.

This type of study would require four data elements linked at the patient level. First, we'd need information about the exposure of interest -- in this case, salmeterol or Advair -- and that would come from prescriptions or from pharmacy dispensings.

We'd also need to know about the outcome of death and whether it was related to asthma, and that information would come from the death certificate. We would also need information about other medications patients were taking, and that would come from the prescriptions or dispensings, and other markers of

asthma severity to try to get a handle on this confounding by severity. This would include things like emergency department visits, hospital admissions, and clinic visits.

So as I mentioned earlier, the consensus of the working group was to do a nested case control study, and I'd now like to walk you through the basis of the basics of the study design.

The green circle represents the cohort in which the study is nested and this is a defined cohort of patients with evidence of persistent asthma who are eligible for controller therapy, most of whom will be on controller therapy of some type.

From within this cohort, all the asthma-related deaths would be identified and these would be identified as the cases, shown in the yellow box on the diagram. We'd next select controls, who are patients from the same cohort, who are at risk, but who did not experience a fatal asthma event, and these controls could be matched to the asthma death cases on a number of important factors, such as age, gender, and year.

We would then look back in the longitudinal record of the cases and controls to assess specifically if and when they had been prescribed Advair and this would allow us to quantify the association between Advair and fatal asthma.

What's very important to understand here is that the Advair exposure truly did happen before the outcome. In this situation, the use of automated prescription data is an important strength, because it helps avoid recall bias, which, as you know, is the traditional criticism of case control studies, where people remember things differently after they've had their heart attack or a child with a fetal malformation.

That's not a case, of course, in a fatal asthma study, where people aren't remembering the medication that they were on. But more importantly, in the longitudinal record, you're recording what people were taking.

So this kind of a study is free of that bias and really should be seen as a longitudinal study, even though it includes these words "case control."

Now, confounding by severity is so important to this effort that I'd just like to spend a few more minutes on this. I think all would agree that patients with evidence of more impairment or more markers of severe asthma are at higher risk of asthma-related death, and these concepts are clearly stated in EPR-3.

Again, according to EPR-3, people with more severe asthma are indicated for combination therapy with ICS and a LABA. So as a result, it's very important to control for these associations to obtain a true estimate of the risk associated with adding a LABA, independent of the baseline risk of a severe asthma-related event.

In this slide, we see asthma mortality rates per 100,000 among individuals 5 to 34 and the experience of six countries is shown since the 1960s. And for reference, you can see there's a line at the bottom, an orange line, and that's the United States.

But what clearly jumps out of this slide are some fatal asthma epidemics in some countries, but not others. And the one that really jumps out is the one

in yellow from New Zealand in the late 1980s.

Since randomized controlled trials were not feasible to address this epidemic, with something as rare as fatal asthma, investigators in these countries, specifically, New Zealand, launched a series of case control studies to look at whether or not beta-agonists were associated with higher risk of fatal asthma.

These studies generated timely and important evidence that a specific beta-agonist, fenoterol, was responsible for this New Zealand epidemic. Three case control studies were conducted in New Zealand and, as you'd expect, the cases are fatal asthma and these patients were matched to controls, who, in these studies, were defined as patients hospitalized for asthma.

The slide shows the number of asthma deaths in each study, which ranged from 58 to 117. The three studies consistently reported an increased risk for fenoterol, but not for albuterol. And you can see odds ratios of 1.6, 2.1 for fenoterol, and for albuterol, again, no signal of harm.

The fourth case control study was reported in the New England Journal of Medicine. Unlike the New Zealand studies, this case control study was conducted using a large healthcare database from Saskatchewan, Canada, and it showed similar results, again, with an increase in fenoterol.

These case control studies have important implications for today, and not about fenoterol, of course, but in terms of the choice of a study design for this vexing question, but, also, the populations that one would want to study in an FDA-sanctioned effort.

These studies clearly demonstrate the ability of case control designs to identify an increased risk of asthma mortality with a specific beta-agonist drug, should the risk exist.

Now, these case control studies were both sensitive to that risk and they could discriminate between different types of beta-agonist medications, which I think are very important strengths.

A more recent case control study is particularly relevant to today's question about LABA

safety and this was a U.K.-based study by Anderson and colleagues, published in the British Medical Journal.

It's the largest population-based study of asthma death. They included 532 cases of fatal asthma matched to 532 controls, and the controls were defined as patients who had an asthma-related hospital discharge. The study found no increased risk of asthma mortality associated with LABAs, with an odds ratio of 0.97.

Now, the investigators were clever about this issue of confounding by indication and confounding by severity and they stratified to look at what they called the severe subgroup, in the same manner as the New Zealand studies, by restricting the analysis to those with a recent hospital admission and when doing so, the LABA odds ratio was reduced to .70, with a 95 percent confidence interval upper bound of 1.39. So this level of precision would argue against a risk of 1.40 or higher.

Moreover, these findings are actually, of course, quite generalizable to clinical practice, since the study was based on patients receiving

routine medical management, using their medications as patients do.

It's important, also, to note that at the time this study was done in 1994 to '98, those data, at that time, about 95 percent of the patients receiving a LABA were also prescribed a concomitant inhaled corticosteroid.

So what can we conclude from these case control studies? I do believe firmly that the case control methodology is an efficient method to investigate the risk of asthma mortality associated with these medications and that the issue of confounding by severity can be addressed both in the selection of controls, through multivariate modeling, and through stratifying the analysis on markers of chronic asthma severity.

In our specific situation, we will want to look at variables that indicate the level of asthma severity or control and that could be looked at in an analysis to control for this confounding. And we looked to EPR-3 to organize these thoughts and to inform the choice of these markers.

In using observational data, of course, it's important to recognize that you won't have every variable, but you will have a lot of variables and ones that are very closely linked to both Advair use and fatal asthma.

For example, we'll have short-acting beta-agonist dispensings, which is a very good proxy of symptoms. And frequency of SABA use has been associated with risk of serious events in prior epidemiology studies.

We'll also have exacerbations, as measured by hospitalizations, ED visits, and oral corticosteroids bursts. We'd also have several other important factors, such as co-morbid diagnoses and medications, which can affect compliance or prognosis; for instance, using three or more controllers for asthma, which is an indicator of more severe asthma; being referred to a specialist or having lung function testing, which are markers of increased care.

So most accept that these markers are associated with a risk of asthma death and they're clearly related to the likelihood of being prescribed

Advair. So they are very important confounders to adjust for in a future observational study.

So in this slide, it shows power calculations for this proposed nested case control study. And I'll draw your attention to the blue squares, which are based on an estimate of Advair exposure of about 15 percent.

Now, this estimate is based on analyses of large U.S. healthcare claims databases for persistent asthma and takes into account several factors. One is variation in patterns of prescriptions of Advair over this time period. If you think back in 2002 how people were being treated versus now, it's not going to be the same.

There is also heterogeneity across health plans and there's also, perhaps most importantly, less than perfect adherence to controller medications. We know that if you prescribe 12 months of treatment, on average, people take about four. So all of these affect the exposure time of a patient to the medication.

Well, if you set the power at 80 percent --

if you like 90 percent, you just slide over to the end here -- but at 80 percent, we'd need about 1,500 cases in order to detect a 25 percent increase or an odds ratio of 1.25, and this is the same level of risk that you heard from Dr. Knobil in her presentation.

This estimate is, of course, sensitive to higher or lower prevalence of Advair exposure. For example, if we assume that 10 percent are exposed to Advair, which is shown in the white line, then the number of cases climbs to 2,000. If the exposure is more common, say, 20 percent, shown in yellow, then it drops to about 1,200. And, again, if you want to use 90 percent power, that would be 1,500. So we're sort of bouncing around the same number of cases.

To put this in perspective, Dr. Knobil also showed the mortality trends in the United States in 2007, when there were a grand total of 3,300 total deaths from fatal asthma in the U.S. that year.

So for the target population of 4 to 64, the number is even smaller. It's actually about 1,500 deaths in a year.

So how do you do this? Well, you do this by

combining data across many years from many different plans and, in doing so, conduct a robust study of the relationship between Advair and risk of fatal asthma; not fatal asthma intubation, hospitalizations, but, actually, the question that has brought us here today, which is this issue of do LABAs increase risk of fatal asthma. And I think we have to keep sticking with that question, because, again, that is why we're here.

In fact, if you look at all of these different datasets that are available, and this was part of the feasibility assessment of the working group, we looked at all these across the U.S. and Europe and you can see here that with so many datasets, you actually could, by combining 70 million people covered, reach approximately 1,500 or 1,600 fatal asthma cases. It is possible. It is doable.

As I mentioned at the start of my presentation, there are these ongoing federally-funded initiatives to increase the networks with longitudinal patient data to do precisely these kinds of observational studies.

If you look at these years of 2002 and 2008,

as we've done here, again, it looks like there will be at least 1,500 cases. This would be sufficient to address a 25 percent increased risk associated with Advair use in patients aged 4 to 64.

So on this final slide, I want to show a draft timeline for the proposed study. The first year would include finalizing the standard protocol and creating these asthma cohorts and these different large databases.

Cases then would be identified through linkage with cause of death information; and, in the second year, we would select controls, assess exposure, develop covariates, and assess power.

Big step here. If the power was deemed insufficient to exclude a risk of 25 percent, which I think seems pretty unlikely, based on all the work I've presented to you, we could certainly discuss potential expansion of the study to identify additional cases, and there are several ways that could be done.

But assuming that sufficient power was available, and I do think that's the most likely, the

second phase would start immediately, which would be to generate risk estimates and look specifically at the association between Advair and our primary outcome of interest, the major signal. Does LABA, in addition to inhaled corticosteroids, increase risk of asthma death?

So estimates then in the final phase would be pooled across the different databases. In summary, based on this information, our working group concluded that a nested case control study was scientifically credible and feasible for the specific rare event of asthma mortality and that such a study could deliver results in a timely manner.

Thank you.

DR. KNOBIL: Thank you, Dr. Camargo. The objective of this advisory committee is to make recommendations to the agency concerning clinical studies which would best inform on whether a LABA plus an ICS is associated with an increased risk of serious asthma-related outcomes.

For our portion of the presentation, we have presented the data and the recommendations that are

specific to Advair. We are all committed to the same goal of improving public health and serving the best interest of patients.

Based on the data discussed today, a randomized controlled trial to study the question of asthma-related death with Advair is not feasible, as millions of patients would be required.

Compromising the study by increasing the risk to exclude or utilizing a composite endpoint would not answer the primary research question of asthma-related death and my concern is that we would be no closer to a clear answer than we are today.

Dr. Camargo described the output from the Asthma Mortality Working Group, which leads to our first recommendation. An observational study is the only feasible approach to study rare asthma outcomes with Advair. A case control observational study addresses directly the safety question raised by SMART, will utilize a clinically relevant risk to exclude, is generalizable to clinical practice, and, as you've just heard, can be completed in a reasonable period of time.

We also recommend a large randomized controlled trial of Advair versus inhaled corticosteroids to better understand the endpoint of exacerbations requiring oral corticosteroids. This study will not directly address the more serious outcomes of asthma-related death, intubations, or hospitalizations, although these data would also be collected, but is clinically relevant for physicians and patients.

This study can also be completed in a reasonable period of time, but only if the proposed labeling does not interfere with patient participation. These two studies would complement each other in answering the questions discussed today and would address the question of whether the assured use of an inhaled corticosteroids mitigates the risk of LABAs that was seen in SMART and would add to the understanding of the overall benefit-to-risk profile of Advair.

Thank you for your attention, and I'd be happy to address any questions.

DR. SWENSON: Thank you, Dr. Knobil. GSK

has kept a little faster than they planned, so we do have a bit more time. And I had to cut off questions in the earlier portion and I thought that what I would do here is give us about 5 to 10 minutes to answer some of those questions that people had following, and then we'll get to questions directly to GSK's presentation.

So, Dr. Platts-Mills, you had a question to the FDA.

DR. PLATTS-MILLS: Actually, it's a question that will go very well to the FDA and to the company. And that is, is this really a severity issue or is this a controlled trial issue?

Neither the FDA nor the company have addressed the issue of the SMART study, which is that in the SMART study, the mortality is really in the first half and it is in the first half of the study where people are being enrolled by telephone that the mortality occurred, significant.

The question is, was that more severe cases, more African-Americans, more people in poverty, or is there actually a risk created in controlled trials?

Is it possible that the reason we're here is that, actually, there is a risk created in controlled trials which is not present in normal practice?

That is, in normal practice, there's another element to what we've been presented. The NAEPP guidelines was presented as a table both by FDA and by the company and had excluded the section that described allergen avoidance.

That is, the NAEPP was very careful to say that at each step, you have to address allergen avoidance. And in view of the results of Rosenstreich, et al, New England Journal and Morgan, et al, New England Journal, showing that in African-Americans, allergen exposure, in particular, to cockroach, but also to dust mite in different areas of the country, is a major element.

Within these control trials, do you avoid normal management? That is, normal management, certainly, in my clinic, would involve addressing these issues regularly.

If we look, again, at SMART, how did SMART achieve a mortality rate, which Dr. Fleming describe

as -- what is it -- 41 events per 1,000?

DR. FLEMING: That was death, intubation.

DR. PLATTS-MILLS: That's intubation.

DR. FLEMING: Death was 12. Death was 11.2 per 10,000.

DR. PLATTS-MILLS: But it is very difficult to understand how it achieved a mortality rate that it did, because it's much higher than the national average. And we have always assumed --

DR. FLEMING: Much higher than the national average of moderate to severe types of patients entered into the trial?

DR. PLATTS-MILLS: That's right. We don't know. We don't. That's why I said, is this a severity issue. That is, the design of the controlled trial would decide whether you enrolled severe cases or not, or is it an issue of whether controlled trials can actually create a risk that doesn't exist normally?

DR. SWENSON: You can go ahead and give us a quick synopsis of your thoughts.

DR. KNOBIL: Yes. I'll try to answer some

of those questions. I don't know that all of them are answerable. So SMART was conducted in a time when, as I mentioned, the use of inhaled corticosteroids for the treatment of asthma was as common as it is today. It was also started in the time when asthma mortality was also higher.

So there are a couple of factors here that are working that I don't know that we can pull apart. As you pointed out, the enrollment for SMART in Phase 1 was by a media campaign. So the patients that saw the TV commercial would call a number, an 800 number, and they would be directed to a center that was closest to their home.

Now, many of these patients, probably most, did not go to a physician that knew them or was following them for their care. And so that may have also played a role in the higher rate of events that we saw in Phase 1.

In Phase 2, the patients -- because enrollment waned in the first part, we had to step back and find different ways to enroll. So we started in Phase 2 recruiting physicians and their patients

already in their practice. So these were patients that were known to the physician investigator and who had been followed by that person.

So as a result, there were fewer events; maybe not as a result, but associated with that, there was a fewer number of events. And it could be that these patients were just better managed.

So to answer your question about whether randomized controlled trials worsen asthma care, in our experience, the rates of events, symptoms, whatever you want to follow, actually goes down, even if you treat a patient with a placebo, because I think, often, they get better care in a clinical trial.

I think SMART was a special case of a study design that we probably wouldn't repeat today, because of some of the limitations that we saw.

Did I answer most of your question?

DR. SWENSON: Dr. Fink?

DR. FINK: A comment and a couple of questions. Comment, I agree with the FDA's stance that we should use fixed combination products in these

trials, but to say that that's based on compliance in children and adolescents is a little misleading, because children are actually more compliant in taking their medications than adolescents or adults.

Studies show that, typically, children between 4 and 11 have 40 to 50 percent compliance rates versus 20 to 30 in adults. So I agree with the recommendation, but it shouldn't be based on compliance.

Questions. A 3-month trial does not take into consideration seasonality of asthma flares. I couldn't find any background data on seasonality of asthma deaths. But since regionality would increase the sample size, it would seem that seasonality also would, unless a 1-year trial was undertaken.

This may be particularly important in pediatrics, where, if a 3-month trial design is used, the majority of the enrollment will be predicted to take place during the summer when kids are out of school and will not include the wintertime asthma season, with viral infections as triggers.

My other question, on the Salpeter trial,

how much faith can you put in a meta-analysis when they are using different studies that have over a 10-fold difference in increase in risk? There was asthma death, intubation, varied from 1 in 126 in one trial to 1 in 1,834 in the highest trial.

When you have that great a variation in the same endpoint, how much faith can you put in the meta-analysis? It really implies that there is a difference in trial design or enrollment criteria rather than a true meta-analysis, because in a true meta-analysis, you should have a clustering of the outcomes along a common point.

DR. SWENSON: Andrew?

DR. MOSHOLDER: Just a couple thoughts on the Salpeter, et al, paper. I guess, to me, looking at the strengths is not -- of the association is the consistency. It's very few events in the ICS without LABA arm. So even though it's based on a small number of events, these are rare events.

That's why, from trial to trial, the rate will be variable, because those rates are all based on a single event. But in every case, that single event

is occurring on the LABA arm and that's sort of the strength. It's as if you're flipping a coin six times in a row and it comes up heads each time, that's a clue that there is something going on.

So that's just sort of conceptually. Then I think, statistically, we can look in the paper, but I believe there was a test for heterogeneity, which showed that it was valid to pool the data into a meta-analysis, which is sort of the statistical criteria used.

DR. SWENSON: Dr. Carvalho?

DR. CARVALHO: Thank you, Dr. Swenson. I was interested in a comment made by one of the agency speakers regarding the optimal pediatric age defined as either less than 12 or less than 18.

Although we're all aware of the implications for steroid use in that population, I wondered what the agency's thoughts were on these age definitions.

DR. MCMAHON: This is Ann McMahon. I was the one who made that comment and I was mostly bringing that up to talk about this issue of optimal sample size and powering for the adolescent age group.

So I just wanted to make sure that that concept was thought about, but it certainly -- I think that the less than 12-year-old is a little more standard.

DR. CHOWDHURY: Just to address that point. In our briefing document, if you see, when we use the cutoff of age 12, we actually write in the document to have a presentation of the adolescent patient population, meaning age 12 to below 18.

DR. SWENSON: Dr. Kramer?

DR. KRAMER: This is a question from earlier. I think the question that was raised about whether we're at a stage of equipoise is, I think, a critical question. And I think my confusion is having been at the December -- participated in the December 2008 advisory committee, it was pretty clear that there was consensus, when LABAs are used alone, that there's an increased risk.

But it wasn't clear, mainly because of the design of the SMART study that we've heard better explained this morning, what the mitigating effect of ICS would be.

Now, what I'm confused about is that -- well, at that time, a large proportion of the FDA's meta-analysis was contributed by these earlier studies, when the treatment of asthma, the practice in treating asthma was quite different and fewer people were actually taking required ICS.

I was really struck when I realized that in the SMART study, that only 48 percent or so were taking baseline ICS.

We now have presented to us today these new meta-analyses, and we were given a copy of the Salpeter article late in our briefing documents, but that study also continues to include -- of the 36,000 patients, 26,000 are contributed by SMART.

I'm not a statistician and maybe the statisticians can help me a little here, but, in particular, there's a reference to the use of LABA with variable corticosteroid. So my first assumption was variable might mean that it wasn't a fixed dose combination, it was variable what you would use.

But, no, the definition of variable in this was that corticosteroid was used in the study in less

than 100 percent of patients. So in that study, with a large proportion of the patients in this meta-analysis, 52 percent of patients were not taking, even at baseline, any inhaled corticosteroids and then throughout the study, were not followed for their use of ICS.

So what I'm confused about is why we're continuing to use, quote, "new meta-analyses" that are predominantly impacted by the old data, where practice was different. And I very much want to be careful about signals, but are we continuing to rehash the same data?

Then, finally, in terms of this equipoise, it just seems so stark to me that the data on Advair that we had presented this morning and even were presented at the last committee really don't raise a safety signal, and yet we're talking about doing studies in 80,000 patients, a million patients, to exclude a signal that hasn't been shown.

So I'm just really having trouble understanding why we don't have equipoise.

DR. MOSHOLDER: All right. Let me just take

a crack at that. I guess going back, first, to the Salpeter paper, I think the important part in the forest plot that I showed is the section 2, in which case, all of the subjects in those trials received concomitant corticosteroids. And you're right, the SMART study is actually represented in section 1, which is trials in which patients may or may not have had concomitant steroids.

But really, sort of what's new is the analysis in the trials where all patients had concomitant steroids. And if you look in the text, it says, "If all trials with and without events are included in the analysis," there are 14 events in 35,000 patients treated with combined therapy and three events in 29,000 patients treated with corticosteroids.

So that's the bottom section of that forest plot. So that's sort of what's new for this discussion. And Dr. David Graham will elaborate.

DR. GRAHAM: Well, just one other point. It has to do with the use of a non-inferiority trial to test for harm and look at what the null hypothesis is

that's being proposed. And the null hypothesis, which is what we believe the state of nature to be at the start of the study, is that LABA plus ICS increases the risk by greater than or equal to some delta that we were talking about.

So one of the questions that comes up to us in terms of equipoise and ethics of the study is, what would an informed consent look like for a study like this, where we say our baseline hypothesis is that LABA plus ICS will increase your risk by more than this delta; we want to do a study to confirm that that's true; will you enroll in the study.

We think that that's something that needs to be explicitly debated and discussed.

DR. SWENSON: Dr. Fleming?

DR. FLEMING: I have a couple of comments, but really leading into a question for the sponsor. So would you like me to wait then for the FDA discussion to end?

DR. SWENSON: No. What I'd like to do -- I should get agreement by the committee here -- is that if we continue on here for another 15 minutes, I think

we'll be able to cover some remaining questions, as well as more questions to GSK. And we'll still have our hour for lunch and then we'll begin straightaway with the next sponsor's presentation, if that would be satisfactory.

I see no great dissent. So, Dr. Fleming?

DR. FLEMING: So a couple of parts to my comments and then leading into a question for the sponsor, and that's going to lead to their slide A-25, if you can put that up.

So one of my earlier comments to the FDA is that, from my perspective, everything is benefit-to-risk and while there is a signal, it's a signal on the most important elements that are fairly rare, and, therefore, the absolute increase matters, but understanding quite clearly what efficacy is.

Specifically, the efficacy issue is what does the LABA plus ICS add to ICS in properly controlled trials for efficacy is something that we have to well understand in order to be able to, in my belief, establish what is an acceptable margin or what is a proper margin for what's unacceptable increase in

these major asthma-related death, intubation, hospitalization outcomes.

Now, one of the things that I wanted to probe a bit with the FDA, but I'll just state it as a comment, is there are going to be differences, substantial differences in what event rates are.

So if you take a look at asthma-related death, the FDA analysis is talking about 3 per 10,000. In SMART, it was 12 per 10,000. For asthma-related death and intubation, in the Salpeter, it's 6.4 per 10,000. In SMART, it was 41. Differences of factors of 4 to factors of 8.

It could be ICS use. It could be other selection factors. It could be a lot of things. I don't understand what all of them are, but it's one of the reasons why randomized trials are really important.

Observational studies have a role. Observational studies have a role when you're looking at something incredibly rare and the only thing that's going to capture your attention is a really big odds ratio increase, such as an odds ratio of 10.

So with rotavirus, in its inception, it was increased by a relative rate of 10. For Tysabri in Crohn's Disease and MS patients, the PML rate was increased by a relative risk of 1,000. I can get those answers without a randomized control.

But I need a randomized control when what I care about is more in the range of no increase versus a 1.25 versus a 1.5. And so the argument that we're going to be able to use in observational study to drill down on no increase versus 1.25, to my way of thinking, is treacherous, because selection factors, differential use of ICS, differential selection in patient severity, seasonality, regionality, all of these things can readily be factors more than 1.25.

So my sense is the only sensible argument for observational studies is if we're saying all we care about is a relative risk of 10 or more on the most rare events, which might be true if the overall benefit is sufficiently significant.

So the argument that was given here, with some strong emphasis, is we need to rule out 1.25 and the context that was briefly alluded to here was what

the FDA has done in other settings right now in Type II diabetes or in the Cox 2 inhibitors in OA and RA patients.

In those settings, the relative risks that we have had to rule out are in the 1.3 to 1.33 range. But just take a moment in PRECISION in the Cox 2 setting, where the rate of events is 1 per 100, 1 percent. That's 100 per 10,000.

We've had to rule out a one-third increase. That's ruling out an excess of cardiovascular death, stroke, and MI of 33 events per 10,000. Why is that allowed? Because compared to nonselective NSAIDs, you're preventing 50 GI ulcers and you're getting more broad overall coverage for analgesic benefit.

In the Type II diabetes setting, we have recently gone to a 1.3, ruling out 1.3, as the sponsor has indicated. Where does that come from? That's a 2 percent annual baseline rate. That's 200 deaths, strokes, and MIs per 10,000. Ruling out 1.3 is ruling out an excess risk of cardiovascular death, stroke, an MI of 60 events per 10,000.

Why would you allow that? Why would you

allow those hard, macrovascular complication endpoints? Because there's strong evidence, with glucose control, you're getting microvascular benefits of nephropathy, retinitis, neuropathy. That's the tradeoff. That's how the logic went.

Well, if I follow the sponsor's logic here, where the events are 3 per 10,000, if we have to rule out 1.25, that's arguing that it's unacceptable to have an increase of .75 events, less than 1 event per 10,000.

These odds ratios in RA/OA with COX-2s aren't ruling out 1 per 10,000. They're ruling out 33 per 10,000. In Type II diabetes, the 1.3 isn't 1. It's 60 per 10,000.

So my sense is what the sponsor is telling us here is the benefit is so marginal in this setting, that if we have even 1 excess event per 10,000, this is unacceptable. That's the only logical basis for this margin.

So if, in fact, this is what they're saying -- and, by the way, SMART is suggesting 14 excess events, in that context, per 10,000.

My question is, why, in fact, isn't it acceptable to be more lenient? I never thought I'd be arguing for a sponsor to take a bigger margin.

[Laughter.]

DR. FLEMING: Why, in this setting, isn't it acceptable to be using -- I get it for hospitalization. I want a margin of 1.5, because that's 45 excess events. But for asthma-related death or even asthma-related death/intubation, if I have a margin of 4, why is that important?

I reduce from having to have 844 events to 22 events. It takes 1/40th the amount of information to rule out an excess of 4 than 1.25. Now, rarely do I argue for 4, but an excess of 4 here would still mean that we're ruling out more than 9 death/intubation events per 10,000 people. And it's more rigorous than the margin of 1.3 in Type II diabetes and 1.33 in COX-2 inhibitors.

So if you argue this is what we have to have, then I do accept the arguments that we don't have equipoise, because I'm not at all confident it's not about 1.25. And you're right, we can't study it.

But I don't understand, for asthma-related death, asthma-related intubation, why it wouldn't be acceptable to rule out 4, in which case, now we can do this with a 40 to 50,000-person study.

DR. SWENSON: I'll let GSK have a chance at that.

DR. KNOBIL: Again, I'll try to answer all of the points raised. The fundamental issue that we're facing is the one that you've already raised eloquently, is that the rate is very low. And that is the problem when we want to rule out the risk of asthma-related death.

So this argument here was in general and was more about hospitalizations than asthma-related death. But -- but let me finish.

DR. FLEMING: Yes. No. Go two slides later. No, it isn't. Please just show A-27, because then you threw at us 4.5 million people.

DR. KNOBIL: Yes. So then I showed the margins. I showed the same margins.

DR. FLEMING: So you were giving us the 4.5 million argument in the context of 1.25 for death

rate.

DR. KNOBIL: Yes. So even if you decrease the -- or increase the level of risk to exclude, you could decrease the number of events that you need. Absolutely true.

However, if you only have 22 events and you have -- let me think of a number -- 17 in one and 15 in another, there are people -- because you can't exclude a certain risk -- who will still view that as evidence that there is an increased risk with LABAs and asthma-related death.

We have a lot of data that have been proposed today from meta-analyses, mostly from meta-analyses, and people, I think, have taken meta-analyses as the gospel, that there is an increase in asthma-related death when you add a LABA to an ICS, and there's a lot of emphasis placed on those data.

I think that if we are going to put this question to rest, we have to include a reasonably low level of risk to exclude.

Now, to your other question, we have a lot of efficacy data. There is a great deal of benefit to

Advair in patients with asthma.

For the interest of time, we couldn't go over the whole dataset that we have. But not only is there an improvement in lung function, an improvement in symptoms, more patients achieving total control or well controlled asthma, patients being able to maintain normal lives is what patients experience every day.

Asthma is largely an outpatient disease. It is not a disease that has frequent hospitalizations or frequent serious adverse events. This is something that affects people every day of their lives.

What you want to do for patients with asthma is you want to get them as close to normal as possible, and we have data to support that. I don't know if you've looked at the GOAL study, which Advair treatment improves total control over steroids alone. It improves the proportion of patients who were well controlled over steroids alone. There's improvements in quality of life. There's improvements in daytime and nighttime symptoms. And when you take patients off of Advair, you see all of those manifestations

come back in many patients.

So this setting of this advisory committee has not allowed us to actually go through the total benefit-to-risk argument that you're asking for.

DR. FLEMING: Can I drill down? Because I know my time is limited. I'd like to drill down on the essence of my question.

The data that are put forward from several sources that, to me, are the most reliable indicate a signal. Do I understand reliably what the true excess risk is for asthma-related death and intubation in the setting where you're adding on to ICS? No, I don't. But I am very concerned about the signal.

Yet, my sense about this is I don't believe that 1.25, if it's the truth, is unacceptable, although I would like patients and caregivers to be informed so they can make an informed judgment.

My concern is that with Salpeter, 3.65, and other estimates that generally indicate an excess. My concern is I need to understand whether there is an excess and I need to understand.

Eventually, I believe, to come up with this

margin, we have to make a judgment, as we did in Type II diabetes and as we did in OA and RA with COX-2s, as to how much we would accept for an increase in the context of a wide fraction of people getting benefit. And my point to you is just I would think it would be mother and apple pie to you.

A 25 percent increase isn't necessarily the largest unacceptable for asthma-related death, asthma-related intubation, when those events are only occurring at 3 to 6 per 10,000. It readily could be that we would have to rule out a fourfold increase, in which case, if we draw that conclusion, it is entirely feasible to do a trial that would rule out a 30 percent increase in hospitalization and a fourfold increase in asthma-related death, which, by the way, is what SMART essentially was doing in a balanced way.

Is it, in fact, from what you just said about all the efficacy that you see, that I'd like to better understand, isn't it your argument that even if it's a 25 percent increase, that could be acceptable in a patient choice scenario; that what's ultimately the upper limit of what's unacceptable for these rare,

but profound events of death and intubation, could be more on the order of a three to fourfold increase?

Would you disagree with that?

DR. KNOBIL: Well, I'll let Dr. Camargo also comment on that. If we were to demonstrate a three or fourfold increase with Advair versus ICS, I don't think that would be reassuring at all.

DR. FLEMING: I didn't say demonstrate that.

DR. KNOBIL: And, in fact --

DR. FLEMING: I said rule it out. I said is it that the margin here is what you're ruling out, not what you're demonstrating.

DR. KNOBIL: The other issue that we're dealing with is that we have seen no deaths on Advair in 10 years of clinical experience. So we're imputing a rate here.

DR. FLEMING: But it's a little bit of absence of evidence is evidence of absence, because the expected number of deaths for the number of people you have, even though it's rare, it's not inconsistent with what FDA has shown.

What you've shown is the absolute increase

is not significant. But what we don't know is what the relative increase is relative to the overall event rate.

DR. KNOBIL: The only other thing I'll say to that is that the level of evidence that we have with the Advair trials is about equal to the exposure that we had with Serevent in SMART.

So when you're looking at evidence, there are different ways of looking at it and, as we've seen before, there's no --

DR. FLEMING: But the baseline rate is so different in those two settings.

DR. KNOBIL: -- there's no evidence for increased death or intubation.

DR. FLEMING: But, again, the bottom line is what you're saying is, in fact, reinforcing what I'm understanding, and, that is, when it's so rare, a relative risk could be greater than 1.25 and be acceptable.

So what you're doing is you're putting forward a strawman that we can't study something that actually is far more rigid than what we actually have

to show. A more reasoned measure of what we have to show is studyable.

DR. SWENSON: Dr. Camargo, I think we should let you have the last word here about your trial, your suggestion, and then we'll convene for lunch.

DR. CAMARGO: Well, I won't pretend this will be the last words. I think we all know that. Wouldn't that be nice?

[Laughter.]

DR. CAMARGO: I think you raised some excellent points and let me just go along with your assumptions that the risk may be 3 or 4 for fatal asthma.

Well, I would remind you that the fenoterol studies actually showed risks of 1.9 to 2.1 and the Saskatchewan study showed a risk of 3.8. So it's exactly along the range that you're hypothesizing. And this would be done more quickly, without any of these consent issues, which, I would add, would be greatly compounded by telling patients "You're entering into a study where we think that you will be 3 to 4 times as likely to die."

So I think you made a very eloquent case for why we should do an observational study now.

[Laughter.]

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: Actually, I have one question for --

DR. FLEMING: I would like the final word on that. It is true --

DR. SCHOENFELD: -- Dr. Camargo before he gets down. So the two questions I have have to do with sort of technical details of the case control study, which they're not too technical.

But how do you deal with the fact that the control group in the case control study have to be people on ICSs, basically? So it's not just any asthma patient. It has to be someone who is getting ICSs. In other words, we're focusing on that, on those populations.

The other question is that it may be that asthma deaths may over-represent people who are getting sort of inadequate medical care, that are not under care of a doctor and so on, and they wouldn't be

getting Advair either.

So there's kind of a second level of confounding, which is confounding, I guess, by neglect, and how you would deal with that kind of confounding.

DR. CAMARGO: Well, you raise a lot of issues. To step back even further, we see asthma mortality declining in this country and it's not possible or credible and I don't think anyone would make the case that the majority of those people are on Advair. They're not.

But we want to do a study to find out what happens when you add a LABA to a baseline inhaled corticosteroid and the study that I proposed would take people with persistent asthma, and you could actually restrict it to people who are on inhaled corticosteroids and you can further restrict it to people who had filled out X number of dispensings per year. And you can see that when you pool together all of this data, you're going to have roughly 1,500 cases, maybe 1,000 cases.

But if we're shooting now for an odds ratio

of 3 to 4, it's going to be easier to see whether or not there's actually a signal. In fact, you could even go further and try to look at subsets and see whether or not it's more in one group or the other.

So, again, I don't see these as arguments against doing the observational study. It will be a little more restricted.

DR. FLEMING: Could I have just 10 seconds to respond to that?

DR. SWENSON: Ten seconds, Dr. Fleming.

DR. FLEMING. Ten seconds, 10 seconds. Absolutely. What you're saying is look at how the rates have reduced over time. What we look at when we look at SMART rates versus everything that's emerged later, there are factors of 4 to 7 difference overall.

That's exactly telling us that we can't use observational studies for factors of 4, but we can, in fact, study a factor of 4 with randomization.

DR. PLATTS-MILLS: Ten seconds is up.

DR. SWENSON: I'm going to have to take the chairman's prerogative here.

DR. PLATTS-MILLS: No. He is totally wrong.

He's totally wrong.

DR. SWENSON: This can't be settled in 10 seconds.

DR. PLATTS-MILLS: No, it can be.

DR. SWENSON: And I think we need to just come back --

DR. PLATTS-MILLS: He is not an asthma physician and he is talking about a disease where asthma death can be a random event in a person who is mild and it's an incredibly important event in a benign disease.

DR. SWENSON: Gentlemen, these questions are important and I think we'll have to give them due time. It won't be solved here in such a brief moment.

We'll reconvene at 1:30 for the presentation by AstraZeneca.

(Whereupon, at 12:33 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

DR. SWENSON: Welcome back, everyone. Before we start with the next presentation by the sponsor, I need to read a statement with respect to our sponsors' presentations. And I failed to do this ahead of GSK's, but I think they held to the spirit of it.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsors' non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon outcomes of the meeting.

Likewise, FDA encourages you, at the

beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

I failed to have the opportunity to introduce Dr. David Schoenfeld, who came in just a bit late, and you've heard him already with his epidemiology and other expertise.

So we'll now move to the presentation by AstraZeneca.

DR. BONUCCELLI: Good afternoon. I'm Dr. Cathy Bonuccelli and I am the Therapeutic Area/Clinical Area Vice President of Respiratory and Inflammation at AstraZeneca Pharmaceuticals.

I want to thank the FDA and the advisors for the opportunity to share AstraZeneca's thoughts regarding the design of a feasible post-marketing safety study to inform the question: does adding a long-acting beta-agonist, or LABA, to an inhaled corticosteroid, ICS, increase the risk of serious

asthma-related events compared with treatment with ICS alone?

AstraZeneca has consulted with multiple experts during the course of our preparations and have brought some of these advisors with us today to provide additional expertise during our conversations here.

Dr. Gene Bleeker, from the Center for Human Genomics and Personalized Medicine at Wake Forest University; Dr. Gary Koch, Professor of Biostatistics, from the University of North Carolina; Dr. Robert Levine, Professor of Internal Medicine and Senior Fellow for the Interdisciplinary Center for Bioethics at Yale University; Dr. Malcolm Sears, Professor of Medicine at McMaster University; and, Dr. Rob Silverman, Research Director for the Department of Emergency Medicine at Long Island Jewish Medical Center and Associate Professor of Emergency Medicine at Albert Einstein College.

This is what we will cover today. In my introduction, I will take you through the background for today's meeting, including the assumptions that

informed the AstraZeneca briefing materials. I will then briefly review the recently released FDA label concept changes and describe, at a high level, how this information alters the context for designing a clinical study.

After my introduction, Dr. Kevin Carroll will review general statistical considerations, including the key determinants of sample size. Thereafter, Dr. Tomas Andersson will take you through AstraZeneca's thoughts about a potential study design for Symbicort, review some of the key study design considerations, and describe the potential impact of the agency's proposed labeling concept changes.

Finally, I will conclude with AstraZeneca's recommendations to the advisors.

AstraZeneca's LABA-containing product in the U.S. is Symbicort pMDI. The ICS component of Symbicort is budesonide and the LABA component is formoterol. Symbicort received FDA approval for the treatment of asthma in 2006 and was launched in the U.S. in 2007.

The current asthma indication for Symbicort

is shown here in yellow; that is, Symbicort is indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older. The label also specifies that Symbicort should only be used for patients not adequately controlled on other asthma controller medications, for example, low to medium dose ICS, or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

In December 2008, the joint advisory committees voted to reaffirm the positive benefit-risk of Symbicort for this indication.

There are two approved doses for Symbicort, 169 and 329 micrograms twice daily, indicating the budesonide and formoterol doses, respectively. The most commonly prescribed dose of Symbicort is 320 micrograms of budesonide and 9 micrograms of formoterol twice daily.

Of note, the dose of formoterol is the same for both Symbicort doses. It is the dose of budesonide that varies. This allows physicians to increase or decrease the ICS doses needed, consistent

with asthma treatment guideline recommendations.

At the December 2008 advisory committee meeting, AstraZeneca had the opportunity to present data on the benefits and risks of Symbicort. Although we will not be reviewing that data again today, I want to take just a moment or two to remind you what they showed. To that end, the next few slides will have embedded in them slides that were shown in the December 2008 meeting.

First, the data showed that adding formoterol to budesonide improves current asthma control. On the left are results from the landmark FACET study, a study in 852 subjects comparing low or medium dose budesonide to the same dose of budesonide plus formoterol over a 1-year period. A higher score means worse symptoms and, thus, lower is better.

As you can see, the addition of formoterol resulted in a significant reduction in asthma symptoms compared with budesonide alone that was maintained over the 12 months.

On the right is a slide from Study 717, one of the pivotal trials for Symbicort pMDI in moderate

to severe asthma, showing the change in FEV-1 for 12 hours after dosing on the day of randomization and then again at the end of treatment.

After 12 weeks treatment with Symbicort, shown in green, versus the separate components, shown in purple, the magnitude, speed of onset, and duration of bronchodilatation are fully maintained; that is, there is no suggestion that over time, the response to bronchodilator is diminished.

We also showed data indicating that adding formoterol to budesonide reduces future asthma risk. On the left, you can see data from the FACET trial, demonstrating that the addition of formoterol decreases mild asthma worsenings, characterized by increased reliever use, decreased lung function, and nighttime awakenings due to asthma compared with budesonide alone.

In that same trial, as shown on the right, adding formoterol to either a low or moderate daily dose of budesonide significantly reduced the risk of a severe asthma exacerbation, defined as the need for oral steroid treatment or a more than 30 percent

decrease in morning peak flow from baseline compared to treatment with budesonide alone.

Therefore, the benefits of combination therapy on measures of both current asthma control and future asthma risk are substantial.

With respect to data on the risk of serious asthma-related events, at the December 2008 meeting, AstraZeneca showed the results of analyses of more than 23,000 patients from 42 randomized controlled clinical trials with AstraZeneca's formoterol-containing products.

Although not all the clinical trials were with Symbicort pMDI, about 80 percent of patients receiving formoterol also received budesonide. In this large dataset, the overall incidence of serious asthma-related events was low, with no asthma-related deaths and one asthma-related intubation.

There was no increase in the risk of asthma-related deaths, intubations, or hospitalizations in patients treated with formoterol. Asthma hospitalizations occurred less frequently in formoterol-treated patients. This data was

subsequently published in the February 2010 Journal of Allergy and Clinical Immunology.

Following consideration of this and other data, the joint advisory committees voted to reaffirm the positive benefit-risk for Symbicort, as currently indicated. There was no vote from the committees on the benefit-risk of Symbicort in children under 12 years of age, as AstraZeneca does not have an asthma indication in this age group.

To AstraZeneca's knowledge, there is no new data since the December 2008 advisory committee meeting that would further inform the question of risk for serious asthma-related events with Symbicort.

AstraZeneca's first contact from the FDA in follow-up to the December 2008 advisory committee was in October of 2009, when they asked the sponsors of LABA-containing products to consider an appropriate design for a post-marketing safety study. When it was clear that all sponsors were facing similar challenges in designing such a study, FDA offered to meet with the sponsors face-to-face to provide us with greater clarity on their request.

In that meeting, which occurred on December 17th, 2009, the FDA reiterated that their primary question was: does adding a LABA to an ICS increase the risk of serious asthma-related events compared with patients treated with ICS alone?

The agency asked the sponsors to outline a feasible study, acknowledging that the most relevant study might not be feasible and the most feasible study might not be relevant. They recognized that hospitalizations are not a surrogate for asthma-related deaths, but indicated that these events are important serious events in and of themselves.

They had a strong preference for a randomized controlled trial over potential other methodologies and did not specify when -- and indicated that the trial should be done in accordance with our approved label. Although they did not specify when the trial results would need to be available, they stated that 10 years would be too long and expressed frustration that the question had remained unanswered for more than a decade.

The AZ briefing materials that you received,

therefore, assumed that the post-marketing safety study would be done within the current indication for Symbicort. As you know, the agency has recently proposed some changes to the LABA class labeling and the recommended use of combination therapies containing LABAs.

Because the eventual study will need to reflect not the current label, but the label after proposed revisions are incorporated, today, we will not only review the thinking that was in our briefing materials, but will also highlight potential study implications of the FDA label concept changes.

In putting forward the study that we outlined in your briefing materials, there were three considerations that were always central to our thinking; that the trial be ethical to conduct; that the trial generate data that will be relevant; and, that conducting the study be feasible.

Specifically, to be ethical, there must be genuine uncertainty regarding which treatment arm will have the better overall outcome at the end of the trial. This is referred to as clinical equipoise.

To be relevant, the trial must be interpretable; that is, designed and powered to test the primary hypothesis; applicable, in that it provides data that is meaningful in the context of how the product is used; and, timely; that is, answers the question in a meaningful timeframe.

Finally, to be feasible, it must be possible to recruit the appropriate patient population and take the study through to its conclusion in the timeframe required.

AstraZeneca is confident that the study we outlined for you in our briefing materials meets all of these basic criteria; that is, it is ethical, relevant, and feasible for Symbicort, as currently indicated.

The study is ethical, because although there is clear clinical benefit of an ICS-LABA over an ICS alone, there is still some uncertainty within the scientific community with regard to the risk of serious asthma-related events with combination therapy.

It is relevant, because the design clearly

tests the hypothesis. The study population and treatment duration are consistent with the expected and recommended use of the drug and the results will be available relatively quickly, we believe within five years.

With regard to feasibility, the direct relevance of our previous clinical trial experience gives us some level of confidence and we have made decisions with regard to endpoint, level of risk exclusion, and treatment duration, which, collectively, help deliver a timely result.

AstraZeneca was, therefore, hopeful that a single, well designed, and rigorous RCT could answer the question posed by the FDA and provide important information and reassurance to patients and prescribers.

However, as other speakers today have already discussed, on February 18th, the FDA issued a safety communication regarding class labeling changes for LABA products. In that communication, the agency made four recommendations to ensure the safe use of LABAs in asthma.

Of these four, the one that has the greatest implications for the design of a clinical trial is the third, at least the third on my slide; that is, LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. Patients would then be maintained on an asthma controller medication. We'll come back to the challenges this presents for designing a clinical trial later in the presentation.

Despite these recommendations, it's important to note that the agency also reaffirmed that they have determined that the benefits of LABAs in improving asthma symptoms outweigh the potential risks when used appropriately with an asthma controller medication.

Subsequently, on February 24th, Dr. Chowdhury of the FDA published a perspective article online in the New England Journal of Medicine, reinforcing and further clarifying the rationale for the February 18th proposed changes.

In addition to restating the key elements of

the recommendations, the article also provided some additional insights, and I'll highlight just a few of those.

First, and I quote, "The FDA's recommendation that LABA be discontinued, if possible, after asthma control has been achieved may cause consternation among prescribers, since asthma treatment guidelines and current practice focus on stepping down the dose of inhaled corticosteroids." Therefore, the agency acknowledged that their recommendations are not consistent with current evidence-based asthma treatment guidelines.

They also state, "Other than the duration of bronchodilatation, the basic pharmacology activity and clinical effect of LABAs and SABAs are the same. The FDA, therefore, believes it is inconsistent to recommend long-term use of LABAs." In other words, the agency use LABAs as bronchodilators, not controller medications; essentially, extended-release, short-acting beta-agonists.

The article goes on to state, "The FDA will also work with these partners to assess whether

prescribing patterns change, leading to the prescribing of LABAs only with concomitant use of the controller drug, compliance with the recommendations of dual LABA and inhaled corticosteroids, and overall decreased use of LABAs." Therefore, the agency's intent is not just to inform on risk, but to change the way that LABAs are prescribed and used.

So how does this new information change the context for designing a post-marketing safety study? In AstraZeneca's view, the impact is considerable. First, and as I've noted, the FDA's intent with the new concept changes is to fundamentally change the use of LABA-containing products, such as Symbicort. For example, they would like to see these products be used only in patients who have failed stepwise increases in treatment with an ICS alone.

They also want to limit the duration of treatment with LABAs, whether used in combination with ICS or not, by discontinuing LABA treatment as early as possible. This step-down approach is not based on scientific evidence, but, rather, based on concerns regarding the potential serious risks of LABA

treatment. Therefore, it is difficult to know what the expected future pattern of use and its impact on serious asthma-related events will be.

Second, based on those same concerns, the FDA has proposed labeling changes that are unusual in that they do not reflect the benefit-risk conclusions for combination therapies from the December 2008 advisory committee meeting, are not based on new data that has emerged since that meeting, and are inconsistent with current evidence-based asthma treatment guidelines.

Whether IRBs, investigators, and patients will still feel that clinical equipoise exists in this revised context is questionable. As a result, you, as advisors, will need to weigh these uncertainties when making your recommendations on the design for a post-marketing safety study.

AstraZeneca carefully evaluated several options to meet the FDA request of designing a feasible and relevant clinical study for Symbicort that could be delivered relatively quickly. It was our hope that completing such a study would address

any outstanding concerns regarding the risk of serious asthma-related events with Symbicort.

In the end, we feel that we address the request that the agency laid out in the December 2009 meeting. Today, we will show that the study we have outlined is designed to address the FDA's primary question, is feasible, assesses a practical and meaningful endpoint for serious asthma-related events, is a randomized control trial that would be conducted in accordance with the current Symbicort label, and that can deliver results within approximately 5 years.

AstraZeneca's briefing materials and the study outline we will share with you today were based on and successfully fulfill these FDA requests. In the next hour, we will take you through the judgments we made in order to reach a final study proposal that we feel best meets the needs of the agency and of patients and prescribers. However, as we've also tried to highlight, the implications of the proposed changes to label and instructions for use will also need to be considered.

Hopefully, I have outlined for you the

context for the rest of our presentation today and identified some of the tougher issues you will need to deliberate on over the course of the meeting.

Now, I'll ask Dr. Kevin Carroll, chief statistician, to come to the podium to take you through some of the key statistical considerations.

MR. CARROLL: Thank you, Cathy. Over the next 10 or 15 minutes, I will provide a brief overview of the main statistical issues that are pertinent to the design and sizing of a study to address FDA's key question regarding whether adding a LABA to ICS therapy increases the risk of serious asthma-related events as compared to ICS alone.

My hope is that you will find these statistical issues to be both useful and informative to your discussions over the next two days.

The chief determinants of the size of a study to address FDA's question are probably not unfamiliar to the committee. They are the significance level, typically, .025, one-sided; power, typically, 90 percent; the expected event rate on ICS therapy alone; and, a relative increase in risk to be

ruled out.

These, combined, give a standard formula for the number of patients required, which AstraZeneca, GSK, and FDA have used in their determination of sample size. Any differences you may see in patient numbers is not due to any fundamental difference in statistical methodology, but is, rather, due to different choices for the underlying event rate, risk to be ruled out, and treatment duration.

Unsurprisingly, events occurring at very low rates require extremely large trials. For example, an event rate in the region of 1 in 10,000 patients per year, which is in the order of what we would expect for asthma-related death, as I shall show you on my next slide, study sizes approach 1 million patients; so by any reasonable standard, are operationally infeasible.

As the event rate increases to around 1 in 100 patients per year, trial size falls accordingly, though remains relatively large, as we should not forget we are still dealing with a low event rate of just 1 percent per year.

In terms of important sensitivities, the most important factor is the event rate. Decreasing the event rate by a factor of 10 will increase the trial size to the same degree. The risk to be ruled out is also of importance and decreasing this by half will increase the trial size by a factor of 4.

In addition to the event rate on ICS therapy and the relative risk to be ruled out, treatment duration is another very important determinant of trial size. As you can see here, a 3-month treatment duration quadruples trial size relative to a 12-month treatment duration.

Please note that so far, I've considered the event rate, the risk to be ruled out, and the treatment duration separately for the sake of simplicity. If we were, for example, to cut the relative risk ruled out by half and reduce treatment durations, say, from 12 months to 3 months, then the impact would be multiplicative and the trial size would increase by a factor of 16. So that, for example, a 5,000-patient trial would jump to an 80,000-patient trial.

Now, before I look more closely at the important relationship between the event rate and trial size, I just wanted to remind you of the data in our briefing materials on the actual event rates we have seen with ICS therapy in our extensive program of clinical trials with Symbicort.

In terms of asthma-related death and intubations, none were seen in over 6,400 patients who received ICS therapy, giving a 95 percent confidence interval for the true rate of asthma death of zero to 0.08 percent per year, which is consistent with recent data published by Sears, et al.

The rate of hospitalization was higher at 1.5 percent per year, with a confidence interval of 1.1 to 2 percent. And the rate of emergency room visits and hospitalizations combined was approximately double at 2.8 percent per year, with a confidence interval of 2.1 to 3.8 percent.

Now, it's important to bear in mind these numbers, since later on in our presentation, when we'll be looking at possible trial options, a conservative approach has been used, where the lower

confidence limit for the events listed on this slide has been used as a basis for trial sizing.

On this slide, I've reproduced table 1 from our briefing materials. You can find it on page 12 of the AstraZeneca briefing document. The key feature you can see from this table is that for very rare events, as highlighted in orange, occurring at a rate in the region of 1 in 10,000 patients per year or 0.01 percent, trials would typically require at least 800,000 patients to rule out the twofold increase in risk.

Even if the event rate was 10 times more common at 1 in 1,000 patients per year, as highlighted in yellow, a trial would still require over 80,000 patients. And please note that these numbers assume a 12-month treatment duration and reducing this to either 6 or 3 months, with double or quadruple trial size, respectively.

Therefore, very rare events, such as asthma-related death and/or intubations, would likely be infeasible as a primary endpoint in any trial.

On the other hand, for events occurring at a

rate in the region of 1 or 2 percent per year, as highlighted in white, such as composites of asthma-related death, intubations, hospitalizations, and emergency room visits, while trial sizes remain large, they do begin to become somewhat more feasible.

However, even for event rates in the region of 1 or 2 percent per year, it is important to recognize the dramatic exponential increase in trial size that occurs as the relative risk to be ruled out drops below around 2. For example, to rule out a relative risk of 1.3 for an event with a 2 percent annual occurrence would require approximately 31,000 patients.

It's also important to recognize, in practical terms, there is little to be gained in targeting a relative risk lower than 2. To see this, consider a trial, hypothesizing a relative risk of 1.3, with a 2 percent p event rate on ICS alone.

Such a trial would require approximately 31,000 patients and ruling out a 1.3-fold increase in relative risk would simultaneously rule out an 0.5 percent increase in absolute risk.

A 2.5-fold smaller trial, hypothesizing a relative risk of 1.5, would rule out an 0.8 percent increase in absolute risk, and a sevenfold smaller trial of 4,400 patients, hypothesizing a relative risk of 2, would rule out a 1.3 percent increase in absolute risk. So that's roughly equivalent to ruling out 2 in 100 versus 2.5 in 100 as event rates in the larger 31,000-patient trial as compared to ruling out 2 in 100 versus 3 in 100 events in the smaller 4,400-patient trial.

Now, on the previous slide, I looked at the value of increasing trial size in terms of the upper confidence limit and the degree of risk that could be ruled out. The relatively small practical gain for substantial increases in trial size when the event rate is low is further illustrated on this slide by looking at the lower confidence limit in terms of the smallest difference in risk that can be detected statistically, with a p value of .05.

So what this slide shows you is that in a 4,400-patient trial, targeting a relative risk of 2 and increasing risk of 0.8 percent or more, would give

you p less than .05 and smaller differences would not be statistically significant.

Similarly, in a 13,000-patient trial, targeting a relative risk of 1.5, an increase in absolute risk of .5 percent or more would give you p less than .05 and smaller differences would, again, not be significant.

Finally, in a larger trial of 31,000 patients, targeting a relative risk of 1.3, an increase in absolute risk of .3 percent or more would give you p less than .05 and the lesser differences would not be significant.

So what you can see is that a sevenfold jump in trial size from 4,400 to 31,000 patients essentially buys you the orange box. It buys you the ability to detect a slightly smaller absolute risk difference of .3 percent as compared to 0.8 percent, the clinical relevance of which will be discussed later in the presentation.

Now, having, in the past couple of slides, looked at the value in driving for ever larger trial sizes, on this slide, I just want you to take a moment

to review what a 4,400-patient trial, with a 2 percent p event rate on ICS alone, could actually deliver.

Here, you can see that if the observed relative risk in such a trial was unity, then a true relative risk of 2 or more would be comfortably ruled out. In terms of tolerance, the highest event rate that could be observed for ICS/LABA and yet still rule out a relative risk of 2 would be just 2.23 percent versus 1.73 percent. That's an excess in absolute risk of no more than 0.5 percent.

So if an excess in absolute risk of 0.51 percent or more is observed, then the trial would fail to exclude a relative risk of 2, whereas if an excess in absolute risk of 0.49 percent or less was seen, then a relative risk of 2 or more would be excluded.

On the other hand, if the observed relative risk was just a little lower than unity, at 0.85, then, as you can see, a 4,400-patient trial would, in fact, rule out a true relative risk of 1.3. The question then is how likely is it that we would observe a relative risk of 0.85.

Well, in this regard, it's important to

recall the data we presented previously at the December 2008 advisory committee, where a relative risk of 0.62 was seen for asthma-related hospitalizations for ICS plus formoterol versus ICS alone.

Therefore, given the positive prior data, as reproduced here in this slide, where a significant 38 percent reduction in the risk of asthma-related hospitalizations was seen for ICS plus formoterol versus ICS alone, a 4,400-patient trial would, in fact, have 93 percent power to rule out a relative risk of 1.3.

In summary, when discussing possible trial options to address FDA's key question, the main statistical points to bear in mind are as follows. Firstly, the ICS event rate is the key determinant of study size. Secondly, trials for very rare events, such as asthma-related death or intubations, typically require at least 80,000 patients and, hence, are considered infeasible.

Thirdly, for composite events occurring at a rate of around 1 or 2 percent per year, trial sizes

are more feasible, but increase dramatically as the relative risk to be ruled out drops below around 2.

Fourthly, reducing treatment duration from, say, 12 months to 3 months quadruples study size. And, finally, large increases in trial size result in little additional practical gain in terms of the increase in risk that can be detected statistically.

So that's all I wanted to say around statistical considerations. I'd now like to hand over to Dr. Tomas Andersson, Medical Science Director for Symbicort, who will take you through our thoughts regarding possible trial designs to address FDA's key question.

DR. ANDERSSON: Thank you, and good afternoon. Today, I will walk you through the options and considerations leading up to the study design proposal that was outlined in our briefing documents. I will also focus on the implications to a potential study of the proposed labeling changes to Symbicort.

We've been asked by FDA to design a feasible study to address this question: does adding a LABA to an ICS increase the risk of serious asthma-related

events compared to treating patients with ICS alone?

We believe that for the study to be ethical, meaningful, and feasible, it should evaluate Symbicort as currently approved for maintenance treatment in patients 12 years and above. This assumes that Symbicort will continue to be indicated as a maintenance treatment for asthma and that Symbicort will not need to be discontinued as soon as patients achieve asthma control. The study must address a question that's clinically relevant and it must be robust enough to definitely answer the question.

It's also essential that the results of the study will be available within the relevant timeframe, and I emphasize this for two reasons; firstly, because we need to finally resolve this issue that's causing confusion and concern among patients and healthcare providers; and, secondly, because with a very protracted study timeline, there are increased risks to the conduct of the study and to the ability to achieve conclusive results.

In our briefing document, we discuss two main options, either a randomized clinical trial or

observational study alternatives. Since we are not recommending any observational alternative, I will not go into those any further today.

Clearly, from a scientific point of view, a randomized clinical trial is the preferred option. In our view, only a randomized setting can provide sufficient rigor for causality assessment between treatment and event.

However, even a randomized control trial will have specific limitations that we need to be absolutely clear about. There is no randomized clinical trial that's possible to conduct within a realistic timeframe that can provide conclusive information on asthma-related intubations and deaths. These events are simply too rare and must be studied using other methodologies.

But what we do know from official statistics is that asthma mortality is steadily declining both in the U.S. and in many other Western countries.

A common objection to randomized clinical trials is that they are not real world and, therefore, not entirely generalizable. However, it's the best

methodology available and the design proposed is striving to maximize generalizability, for example, by including the full population eligible for Symbicort treatments.

I will now go through the design of a study that fulfills the requirement we set up and that can be performed and deliver results within 5 years. To make a large study like this feasible, it's essential to keep the design simple and only incorporate a few carefully chosen endpoints to address safety and efficacy.

Some aspects of the study design have been more obvious, whereas others have required careful consideration, and it's based on our judgment. We are proposing a randomized, double-blind, 12-month study comparing the most commonly used dose of Symbicort with a corresponding dose of budesonide.

The study population would be adults and adolescents 12 years and above with asthma that's either not adequately controlled on other asthma controller medications, like ICS, or is of a severity that makes them eligible for initiation of treatment

with two maintenance therapies.

So far, the choices we have made were reasonably straightforward. The primary endpoint we propose is a composite of the most serious asthma events, defined as asthma-related deaths, intubations, hospitalizations, and serious emergency department visits. The estimated incidence of this endpoint is 2 percent per year. The study would require 4,400 patients in 12 months' treatment to be able to exclude a relative risk of 2 in the study.

In the study, patients would be allowed to us albuterol for relief of acute symptoms. Also, we propose that it would be allowed to add, in an open label fashion, additional asthma controller medications other than LABAs during the course of the study to obtain adequate control of asthma. We believe that's necessary to be able to maintain patients in the study and to mitigate ethical considerations.

Patients randomized to budesonide alone will receive less effective asthma treatments. As efficacy endpoints in the study, we propose to capture or

consider to capture asthma exacerbations leading to oral steroid courses, need for additional asthma controller medication add-ons, and assessment of current asthma control using a PRO, like the asthma control questionnaire, and capturing overall safety and tolerability by capturing serious asthma adverse events and discontinuations due to adverse events.

We also propose that the study should include a 1-year follow-up of all patients after randomization, regardless of premature withdrawal. It should also include blinded adjudication to specify if an event is asthma-related by an independent committee, and monitoring of the number of events to ensure sufficient power of the study and, if needed, adjusting the study size.

I would now like to go through some critical aspects of the study design that has required careful consideration and conscious choices from our side. I will start with the endpoints.

The endpoint should capture clinically important, serious asthma-related events. These events are important in themselves and should not be

regarded as surrogate measures for asthma-relate deaths.

We recommend an expanded composite endpoint comprised of asthma-related deaths, intubations, hospitalizations, and, also, serious emergency department visits. This represents, in our view, the best means for delivering relevant information within a reasonable timeframe.

It's important to remember that the study is powered for the composite endpoint and not for the individual components of the endpoint. And due to the low event rate, one can anticipate maybe one asthma death and one intubation in this study, and, therefore, there will not be any new standalone information on these endpoints resulting from the trial.

Addition of strictly-defined serious emergency visits is suggested by AstraZeneca. It's based on the rationale that these events, just as hospitalizations, are serious, acute asthma events of clear clinical importance. And there are two main reasons to include them. The first is to capture all

asthma events of a severe nature that can inform the question; and, the second is to facilitate the conduct of a meaningful study.

Emergency department visits and hospitalizations are clinically more closely related than hospitalizations, to intubations, or death. As defined and captured in previous AstraZeneca trials, they occur at the similar frequency, whereas death or intubation is 100-fold less frequent.

Both ED visits and hospitalization represent events of acute bronchoconstriction requiring emergency treatment. Patients coming to the emergency department are significantly compromised in their clinical status and lung function and some of the events lead to hospital admission.

In a clinical trial, these events can be strictly defined to capture only those that are serious in nature, excluding minor events. Also, the events will be adjudicated to make sure they fulfill all criteria.

We propose to use a definition similar to what was done in the AstraZeneca START trial, a

landmark study comparing budesonide to placebo in mild asthma, published 2003 in the Lancet. In that study, emergency department visits were specified as treatments given at a healthcare institution for the reason of acute airway obstruction, where treatment and observation must be administered for at least 60 minutes under the supervision of a physician or a delegate, and treatment with both systemic corticosteroid and nebulized or parenteral bronchodilators must be given during the visit.

This stringent definition was used to ensure uniformity in the 32 countries enrolling patients to the study, and it's also in line with the definition according to the ATS/ERS recommendations for capturing ED visits as part of a severe asthma exacerbation.

In this slide, you see the result from the START study, looking at the effect of budesonide versus placebo in mild asthma. The primary endpoint, as can be seen here, was the composite of severe asthma-related events, defined as hospitalizations and severe ED visits. The main result was a risk ratio of 0.58 in favor of budesonide.

I now show you, in the hashed part of the bar, results of hospitalizations alone. The incidence has decreased to approximately half that of the composite endpoint. The effect of treatment is a risk ratio of 0.55 in favor of budesonide.

Several other AstraZeneca studies looking at Symbicort confirm both the relative frequency of these events and the effect of treatment using the two endpoints.

To conclude, by incorporating strictly-defined serious emergency department visits into the endpoint, we can capture about twice as many severe asthma event as when looking at hospitalizations alone. The effect of treatment is captured in a very similar way. This choice of endpoint enables a study that can provide conclusive results in a shorter time.

We then move on to look at the rationale for the duration of treatment. Once again, it's a matter of choice. A 1-year study duration is suggested by us. We have extensive experience from previous 1-year studies, and we know that events occur at the similar extent throughout the period.

It also means that the full calendar year can be followed for each patient and it can capture seasonal variability. The prolonged treatment will also be more informative of risk than a short trial duration.

A shorter study duration would miss several of the aspects above, such as seasonal variability and information of risk with prolonged treatments. Also, a 6 to 3-month study would require 2 to 4 times as many patients, while still not providing any additional information on risk.

We considered a longer 2-year study duration, but do not recommend it, since event rates tend to decline in the second year of asthma trials. So instead of needing half the number of patients, we would need two-thirds compared to a 1-year trial. And a very long study period also makes it hard for patients and investigators to finalize the study period and withdrawals could be a problem.

We need to carefully consider the consequences of the FDA proposed step-down of LABA on possible treatment. In her introduction, Dr.

Bonuccelli told you that Symbicort improves both the current day-to-day control of asthma and, also, reduces the future risk of worsenings and exacerbations.

So what treatment duration can be used in a study if patients that achieve asthma control need to discontinue Symbicort? To address this, I want to consider when asthma control is achieved and how asthma control should be assessed, and, also, what happens with LABAs are withdrawn from patients that are stable on Symbicort.

These are key results from Study 717, one of the key 12-week studies with Symbicort for U.S. When a patient starts treatment with Symbicort, current asthma control based on lung function is achieved immediately and maintained for the study duration. So one might say that based on lung function control, it's achieved from day one.

Available online in the Journal of Allergy and Clinical Immunology is a comprehensive analysis performed by Bateman and colleagues of thousands of patients treated for up to 1 year as part of the

Symbicort maintenance and reliever study program.

The analysis looked at overall asthma control, incorporating both current control of asthma that we can measure here and now and the future risk of asthma exacerbations.

What you see here is the comparison of patients achieving composite current asthma control, as defined by GINA, incorporating symptoms, reliever use, nighttime awakenings, lung function, and activity levels. It chose patients achieving the goals of treatment as being either controlled, in the lower curves, or controlled-partly controlled, in the upper two curves, over the course of a year.

In the graph to the left, you see that both for Symbicort, in green, and for a higher dose of budesonide, in purple, control is improved continuously over the whole treatment period. It improves more rapidly during the first 2 months, but control is steadily improving with maintained continuous treatment for up to 1 year.

The level of control achieved is higher for Symbicort during the whole study period. To the

right, you see a similar comparison between Symbicort given as maintenance and reliever therapy and ICS/LABA given as a fixed dose, and you see exactly the same picture.

So composite control of asthma is not achieved immediately. It improves gradually with prolonged treatment with Symbicort. However, based on the things we measure here, one could say that after a few months, control is good enough and it may be time to step down.

What's not seen here, however, is the future risk of asthma exacerbations. This is data from the FACET study, originally published by Pauwels and colleagues back in 1997 in the New England Journal of Medicine.

The study addresses what additional formoterol to budesonide does to the future risk of asthma exacerbations. The graph shows the number of asthma exacerbations requiring oral steroid during the 1-year duration of the study.

There were four groups, but I would like for you to focus on the yellow and the orange line. The

yellow line is treatment with budesonide, corresponding to the amount of budesonide in the most used dose of Symbicort. The orange line is budesonide and formoterol, corresponding to the mostly commonly used Symbicort dose.

As you can see, asthma exacerbations are fewer for budesonide/formoterol treatments, it seemed, from the start of the study and the difference between treatments continue to increase during the whole year of the study.

The data gives clear evidence that to reduce future risk of asthma, sustained treatment with formoterol and budesonide for up to a year provides continuous benefits.

In the 2008 ADCOM, we presented data looking at asthma-related hospitalizations in 23,510 patients. The analyses show that the events occur regularly over the whole year and, over time, the risk of an asthma-related hospitalization is continuously lower for patients treated with formoterol compared to non-LABA treatment.

The difference between the groups, once

again, seemed to continue to increase with time. The data I have shown you form part of the extensive evidence that formoterol, when used in combination with budesonide, is an asthma-controller medication, behaving very differently than a short-acting beta-agonist.

Formoterol and budesonide contributes not only to improved lung function, but, also, to overall asthma control measured as improved composite current asthma control and reduced risk of asthma exacerbations.

The time spans in which these benefits are achieved range from the immediate, as for lung function, to continuous, as for reduction of asthma exacerbations. On the contrary, there exists no scientific evidence for the treatment recommendation on stepping down LABAs, as proposed recently by FDA.

Now, we turn to look at what happens with formoterol is decreased or withdrawn in patients stable on Symbicort. There were three studies for Symbicort that formed part of a once-daily program submitted to FDA as part of the original submission

package.

These studies are not primarily designed to study withdrawal of formoterol, but it's the data that best addresses the question. Two of these were performed in adults and adolescents and one in children under 12.

In all studies, patients stable on twice-daily Symbicort was stepped down either to once-daily Symbicort or to the same total daily dose of budesonide given once daily. In one of the studies, there was also a placebo group.

This data is from the study published by Berger and colleagues this year. To be randomized into study treatment, patients had to have stable asthma control during the last 2 of a 4-week running period on Symbicort.

After randomization, patients maintained on Symbicort twice daily remained stable with regards to lung function, as can be seen in the purple line. Patients that were stepped down to once-daily Symbicort, reducing the dose of formoterol, declined in lung function, as can be seen in the green and

orange lines. And patients that had formoterol withdrawn and were put on the corresponding daily dose of budesonide given once daily, shown in blue, declined even further after withdrawal of therapy.

This indicates that even after a month of treatment to stabilize asthma, the benefits of formoterol on lung function is lost when formoterol is withdrawn.

In the study, composite asthma control was measured using asthma control questionnaire, ACQ. An increasing score indicated worsening asthma control. Patients in purple were continued on Symbicort twice daily and maintained control. Patients in green and orange had their dose of Symbicort decreased, and the blue bar showed the deterioration in composite asthma control in patients switched to corresponding daily dose of budesonide given once daily. Therefore, also, for composite control measures, deterioration is seen with formoterol is withdrawn.

So to summarize this section, asthma control based on lung function is gained rapidly and maintained for as long as treatment continues. It

reflects the bronchodilatory effects of formoterol.

Composite control measures are improved gradually and are continuously superior for Symbicort compared to ICS alone. We also see a maintained reduction in exacerbations and asthma hospitalizations for budesonide/formoterol versus budesonide. That's continued for up to 1 year.

Therefore, formoterol, as used in Symbicort, is, by all standards, an asthma controller medication. Since reduction in future risk is not directly measureable in the day-to-day measures of asthma control, it's not evident what would be a general cutoff point when to step down LABA.

The available data show that withdrawal of formoterol after a period of stable asthma control leads to deteriorated lung function and loss of composite asthma control. So after this review of scientific evidence, we strongly maintain that a 12-month study duration is an appropriate choice for the study going forward.

On the other hand, there's no evidence providing guidance for the FDA-proposed step-down in

LABA therapy. It's unclear to us how such an approach can be incorporated into a study that, at the same time, can address the relevant question.

Selection of the relative risk to exclude needs to take into account the clinical context. We used a relative risk number to inform the patient/physician dialogue on individual therapeutic choices.

In general, if the benefit is significant, a higher level of risk can be tolerated. In this particular setting, the balance of benefit and risk is the substantial expected clinical efficacy benefit of Symbicort versus a potential increase in a relatively uncommon adverse event of asthma-related hospitalization and serious ED visits.

Clinically, it's helpful to quantify the relative risk number in a way that's understandable to patients and physicians. Obviously, the best estimate from any study of the real relative risk is the point estimate, the main result of the study.

The confidence intervals can then help us to exclude or to find the limits or the certainty of our

results. So, for example, if we exclude a relative risk of 2, the patient could expect that for an event that would occur in 2 out of 100 patients over a year of treatment, they would know that the potential risk could be 4 or more out of 100 patients.

Regarding the difference in absolute risk, the same study would detect a difference between 2 events per 100 patient years and 3 events per 100 patient years. This information on level of potential increase in risk that can be excluded would be traded off against expected benefits, such as improvement in lung function, asthma symptoms, quality of life, decrease in nighttime awakenings, and need for oral steroids.

To put it in context, again, excluding a relative risk of 1.3 would narrow the level of absolute risk that can be detected. So instead of detecting 2 versus 3 events per 100 patient years, you would be able to detect 2 versus 2.5.

However, to achieve this, the trial would need to be sevenfold larger and it would take almost three times as long to complete. Therefore,

AstraZeneca believes that excluding a relative risk of 2 is reasonable in this setting and has proposed studying 4,400 patients for 1 year to exclude this level of risk.

You must also keep in mind that AstraZeneca has previously evaluated the relative risk of hospitalizations for ICS plus formoterol versus ICS alone, as previously shown today.

In this analysis of nearly 16,000 patients greater than 12 years of age, from 27 clinical trials, the relative risk for asthma hospitalizations was 0.62, with an upper confidence limit of 0.93. Thus, we fully expect that the relative risk in this clinical trial will, again, be less than 1.

If we take the point estimate from this analysis into account, as we heard Kevin Carroll describe earlier, then the 4,400-patient trial proposed by AstraZeneca would, in fact, have 93 percent power to exclude a relative risk of 1.3.

Can we have the next slide, please? Looking at the clinically relevant -- you need to step back in my speech, in the script. It doesn't match. It would

make it difficult for me. Some sort of test probably. Thank you.

I mentioned earlier that very little additional information would be gained from driving the relative risk down from below 2 and that the time to complete the trial would be negatively impacted. This figure illustrates a rough estimate of the additional time that it would take to complete the trial, excluding lower relative risks, as suggested earlier today.

As you can see, while the 4,400-patient trial could be completed within approximately 5 years, and I'm now referring to the colored bars, because they are the ones where parallel studies are ongoing at the same time, a 31,000-patient trial to exclude a relative risk of 1.3 could take more than a decade to complete.

Remember, this represents the difference of being able to detect an absolute difference in 2 in 100 versus 3 in 100 compared to 2 and 2.5 in 100. So AstraZeneca feels that, on balance, the small gain in information from lowering the relative risk to exclude

does not warrant the additional time it will take to deliver the results.

Looking at the clinically relevant population for the study, we have suggested the current U.S.-approved population. At the meeting in 2008, it was recognized that there's particular interest to study children, adolescents, and other populations potentially at risk, such as African-Americans.

Our study will include both adolescents and African-Americans. However, results will reflect the whole population, not the subgroups. Concerning children below 12, Symbicort is not currently approved in the U.S. for children below 12 and there's no approved dose.

Further studies in this age group are in the planning stages, but at this time point, we do not see how can include patients below the age of 12 until an approved dose is obtained.

There are multiple factors impacting the conduct of the study, and some are listed here. When we considered the current design, one potential issue

was the willingness of investigators and patients to participate in the study, where they would be randomized to ICS alone, since the evidence shows that this is an inferior treatment to ICS/LABA combinations.

Other factors to consider are the complexity of the study protocol, the size of the patient population that's available, and the logistical capacity to run the study.

Regarding geographical location, we have proposed a 50/50 split between U.S. and other countries. This is a recommendation that's meant to ensure that we have enough U.S. patients in the study. However, we do not propose to perform the study in the U.S. only, since that would lead to overall slower recruitment.

Finally, if multiple large clinical trials with similar design, competing for the same patients and sites, are ongoing at the same time, it will fundamentally affect the feasibility and conduct of the study.

So based on what we have proposed in the

briefing document, what and when would this possible deliver? The study outlined will provide new data to meaningfully inform the question that's still outstanding in the minds of FDA.

We will not get any substantial new information on asthma-related deaths and intubations. The result we will get can confirm or refute previous data analyzed that shows no increased risk of severe asthma events for Symbicort compared to ICS alone, and the result could be publicly available within 5 years.

However, if substantially larger trials are demanded, it will be impossible to deliver within a timeframe suggested by the FDA, 10 years.

Dr. Bonuccelli already mentioned that the potential implications of the proposed labeling changes could be substantial. I want to close this section on clinical trial design by pointing out just a few of the most potential impacts.

The agency recommends that patients remain on LABAs for the shortest duration of time required to achieve control of asthma -- in fact, the recommendation is when patients asthma control,

discontinue Symbicort -- and have based this recommendation not on evidence, but on concerns about LABA safety.

This very strong stance regarding risk of LABA implies certainty rather than uncertainty regarding the risk for serious asthma-related events. Whereas, previously, the ethical challenge was justifying treatment with an inferior option, ICS alone, a new ethical challenge is justifying 1 year of treatment with a therapy that its use needs to be limited due to safety reasons. How this change in risk will be seen by IRBs, investigators, and patients is not clear.

The changes also introduce challenges into the study design. For example, how do we account for using ICS/LABA for the shortest duration possible and still answer the primary question? If we need to step down LABA therapy once asthma control is achieved, how do we decide when that is and by what criteria to do it? And if we don't design a study withdrawing LABAs when asthma is controlled, how long a treatment period can be justified?

Feasibility depends on multiple factors and several of them are affected by the label changes. The agency has made suggestions for more strict use of these treatments and, as a result, fewer patients will be eligible for treatment.

Finally, the relevance of a clinical trial with a one-year maintenance treatment for a product no longer being indicated for maintenance treatment of asthma is highly questionable. If we conduct the study we outlined and patterns of use change, the trial will not inform clinical practice in a meaningful way.

On the other hand, if we try to design a study that reflects the label changes, the result will be more indicative of risks of changing the prescribing recommendations than that of adding a LABA to an ICS.

So, thus, there's no aspect of designing and executing a study that's not potentially impacted by the proposed label changes.

I now turn back to Dr. Bonuccelli to conclude.

DR. BONUCCELLI: Thanks, Tomas. I'm a lot shorter than him. We started out today by telling you that any clinical trial would need to be ethical, relevant, and feasible, and AstraZeneca believes that the RCT we have outlined meets these criteria.

In December, the agency gave us the task of designing a study that was feasible for Symbicort. AstraZeneca carefully considered various aspects of the study design, made judgments and tradeoffs with regard to endpoint, treatment duration, patient population, and level of risk to exclude, and ultimately described a randomized controlled clinical trial that is feasible for Symbicort, based on its current indication, informs the FDA's primary question, and can be completed within 5 years.

So the study we outlined is feasible. Is it also ethical and relevant? The short answer is yes. We determined that the study design is likely to be acceptable to IRBs, investigators, and patients, because although there is some uncertainty within the scientific community regarding the risk for serious asthma-related events, there is a clear and

substantial efficacy benefit for combination therapy.

The study is also considered to be relevant, because it is designed to answer the primary question with rigor, reflects and is, therefore, relevant to the recommended and expected use of the product, Symbicort, and the results should be available relatively quickly. These comments hold true based on the current label for Symbicort.

To conclude, FDA has asked for and AstraZeneca has outlined a randomized controlled clinical trial that, under current labeling, rigorously answers the FDA's primary question of whether adding a LABA to an ICS increases the risk of serious asthma-related events. It assumes that serious ED visits, like hospitalizations, are relevant, serious asthma-related events in and of themselves.

There is no feasible randomized controlled clinical trial that can rigorously assess whether there is an increased risk of asthma-related intubations and deaths. However, other more frequent serious asthma-related events, such as

hospitalizations and serious ED visits, although not accepted as surrogate measures of asthma-related death, can feasibly be studied.

AstraZeneca believes that the result of such a study will provide new and important information to patients and physicians and will also crucially inform whether the FDA's proposed label concepts, in particular, the discontinuation of therapy after achieving asthma control, are necessary.

Therefore, this study should precede the imposition of those label changes that are not consistent with current evidence-based asthma treatment guidelines or based on any new data.

If the proposed label changes are implemented now, because the spectrum of potential impact is considerable, the ethics, relevance, and feasibility of any potential study will need to be reassessed in the context of the final labeling.

AstraZeneca looks forward to the deliberations of the advisors and to resolving any outstanding safety concerns that might exist for Symbicort.

Thank you.

DR. SWENSON: Thank you. In the just remaining few moments, Dr. Bonuccelli has just asked for a few minutes to reply to some aspects of the Salpeter study that reflects and impacts AZ's position. So I've granted her that, several minutes.

DR. BONUCCELLI: Thank you, Dr. Swenson. So there was so much discussion around Salpeter and we felt we needed to share a few points about that.

The first thing I want to do is give reassurance on a comment Dr. Mosholder made. It is true that in the Salpeter article, it is erroneously stated that three cases of death were not included in the December 2008 advisory committee briefing materials from AstraZeneca.

That statement has been made in error in that article. We have contacted the journal and they will be changing the article to correct that set of statements. So if you printed the article yesterday or got it this morning, I would encourage you to go back and look after that correction has been made.

The three cases were, in fact, in the briefing materials, both in the main section of our materials and, also, in an appendix, and you can look them up. I think those are still publicly available documents.

The other point was the dataset. The three cases of death were not in our FDA dataset because of the criteria the agency gave us on which cases would be included in that dataset, and those three cases either did not meet being defined as asthma-related during adjudication or occurred while off of treatment. So those are the reasons they were not in the analysis, per se.

So I'm going to turn now to Dr. Malcolm Sears and he's going to comment on the methodology and other issues related to Salpeter's article.

DR. SEARS: Thank you very much. My name is Malcolm Sears. I'm a Professor of Medicine at McMaster University, a practicing pulmonologist, with special interest in the epidemiology and management of asthma. And I've been involved in issues around beta-agonist safety since the 1960s in New Zealand, which

is where I spent the first half of my academic career.

I've been invited to this meeting by both Novartis and AstraZeneca as a consultant, and so acknowledge consulting fees and travel assistance from those two companies.

I also hold an endowed chair in respiratory epidemiology, jointly endowed by AstraZeneca and McMaster University.

I want to address the issue of the new data which was alluded to this morning. In fact, we have new publications that have come out in the last few weeks, one from Salpeter and the other in Thorax from Weatherall and colleagues, and there are issues there that have been mentioned in passing that I think need to be clarified for the committee.

Some of you may not yet have read these, but I think it's important to say, firstly, these are not new data. There's no new data there. They are re-presentations of existing data and there are major issues to be addressed in how we look at these.

I'm going to very briefly discuss some of the issues in the methodology, but I want to

specifically focus in on the clinical issue, which is confounding by dose of inhaled corticosteroid.

If we look at the Salpeter paper, from the vast number of studies that are available, Salpeter has reported on 12 trials. Eighty-three trials have been excluded because there were no deaths or intubations and excluded those from the primary. And while, in the discussion, she brings these back in again and says it makes no difference, the methodology used to re-include those studies is questionable and, we would say, flawed.

Another 70 trials are excluded because of duration of less than 3 months. And as we've already heard this morning from the FDA analysis, events in the first 3 months are consistent with what happens further along. There's no justifiable reason that I know of to exclude those events in the first 3 months.

The events that are reported do not appear to be blindly adjudicated and we've just heard that events are reported in those papers, which, in the FDA process, with blind adjudication, were removed.

The analyses are not based on individual

patient level data. They are based on summary level data. And so you cannot explore in this any differences in the exposures, in the prognostic baseline risk factors, and variation and follow-up. This is not available through the analyses presented in that paper.

Finally, methodology, the Peto method for assessing the risks of rare events is considered by many statisticians to be not the best method. There are better methods available, but this paper is based on the Peto method.

So those are methodological issues that you'll want to review and assess. But I particularly want to focus on the question of confounding, because I think this makes the interpretation of the Salpeter data quite impossible, to be frank.

In the 12 trials that are reported, there are five in which she acknowledges that the trial design did not require inhaled corticosteroid. They may or may not have been on it at baseline.

So ignoring those five trials, we're left with seven trials in which inhaled corticosteroid was

used by, we're told, 100 percent of the patients. So these are pertinent to the question that's raised of whether adding LABA to inhaled steroid increases risk.

Salpeter and colleagues state that in four of the seven trials, the same dose of ICS was used in the LABA arm and the non-LABA arm, and that's critical, except when you look at the trials and look at the table in the appendix, it does not bear that out.

My reading of this table, and I've gone to colleagues and conferred and said "Help me understand what I'm missing," but my reading of those tables is that of the seven studies that are there, three do not even give the dose of inhaled steroid in the comparator arm. So we have no certainty that it's the same dose as in the LABA arm.

One very clearly shows comparison of LABA plus low dose steroid versus a 4-times higher dose of steroid in the comparator arm. And the other three studies, there are two doses of inhaled steroid either in the LABA arm or the comparator arm or both, and there's no indication in the analysis of in which arm,

low dose or high dose, these adverse events occurred.

So to answer the FDA's question of what is the risk of adding LABA to inhaled corticosteroid, as has been repeatedly stated, you need identical doses of inhaled steroid in both arms so everything else is equal and then you add LABA and see what is the risk, and the data of Salpeter do not address that at all.

The studies that she has reported on are designed to be studies of efficacy, studies of which regimen of treating asthma is better, and those are valid reasons for doing studies.

So you compare should you add LABA or double the steroids, but those are not studies you can use to assess safety, where you need equal and constant doses of steroids in each arm.

I think there's another interpretation of the apparently alarming risks that have been mentioned, risks of 1.6 going up to 1.8 and even of 3.6, where inhaled steroids are being used, which, I think, has another explanation that is equally or more valid -- I think more valid -- and that is confounding by dose of inhaled corticosteroid.

Unfortunately, way back in the '90s, the early studies with LABA showing that adding LABA gave you greater benefit than doubling the dose of inhaled steroid led to the notion that LABA was steroid-sparing. And so in the way LABAs have been used in many trials and in clinical use is to say we'll add it to low dose inhaled steroids and we'll spare the patient the risk of the higher dose of steroid.

So LABA, in general, has been used with a relatively low dose of inhaled steroid. And when you get into studies where the comparator arm is a higher dose of inhaled steroid, you then have this issue of is the increased number of events you see in the LABA arm because they're on less steroid or because of the LABA.

The notion of steroid-sparing was strengthened by the study performed by Lemanske and colleagues, the so-called SLIC trial, in which they put patients on salmeterol and triamcinolone, and they reduced the dose of steroid by, initially, 50 percent and then took them right off and concluded that you could reduce the dose by 50 percent without losing

control of asthma.

In fact, the number, the percentage of treatment failures on a 50 percent dose was double. It just happened to not quite get to p .05 and so it was interpreted as insignificant; but clinically very significant, because when you take the steroids right off, the risk of treatment failure is fourfold.

So the doubling is on the way up. A halving of steroid led to a doubling of treatment failures. And so when you look at the data that you are presented with in this study, you have to say is the risk really the risk of LABA or is it the risk of inadequate dose of inhaled corticosteroid.

Unless you have studies where you know for certain that the same dose of inhaled steroid is used in both arms and the only difference is the LABA, you can't address the issue.

So with all due respect to the authors, I would say that the study of Salpeter if flawed, cannot be interpreted in the way that it's been interpreted. I'm surprised that reviewers didn't pick up these notions and have them addressed before it got to

print, but it's happened. It will create controversy, but I wanted to give you my, hopefully, balanced perspective on it.

Very briefly, just to mention the other paper that has just appeared in Thorax by Weatherall and colleagues, which is meta-analysis of GSK-sponsored studies, which, very interestingly, shows that when you do all the appropriate meta-analyses in this and look at the use of LABA/salmeterol in conjunction with inhaled corticosteroid somewhere in the background, you come up with an odds ratio of 2.1.

So it sounds a risk, except the lower limit of the confidence interval is 0.6. So it's non-significant. But if you look -- and I think this is the very key point of this, which bears out the issue raised earlier -- if you look at the trials in which you know the same dose of inhaled steroid was used, which, basically, are the Advair trials, there were no deaths whatsoever in those trials, as has already been mentioned.

So I put it to you that you need to very carefully think about confounding by dose of inhaled

corticosteroid before interpreting the new Salpeter data, particularly, and to weigh the risk of adding LABAs to low dose of steroid.

If I was on the guidelines committee, my recommendation would be to remove that add LABA to low dose steroid and move it up to add LABA to moderate dose of inhaled corticosteroid. Then I think we're erring on the side of safety, but not to say don't add LABAs.

So I thank you for your attention.

DR. SWENSON: We're just behind schedule, but I think we have time for a few questions and I'd like to open it up to, first, Dr. Hubbard.

DR. HUBBARD: My questions were previously answered. They were addressed to the FDA. So I have no questions for AZ at this time.

DR. SWENSON: Dr. Krishnan?

DR. KRISHNAN: My question was actually directed at GSK. Is this a good time to talk about it?

DR. SWENSON: If you could hold then, I think, to a later point.

DR. KRISHNAN: Sure.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: So the question I have is that given the data you've shown already, don't you know for sure, based on both your meta-analysis and all your individual studies, that, in fact, the risk of hospitalization, ED visits, and so on, that that risk really is less than -- that the relative risk is less than 2.0?

You showed data that the confidence interval excluded 1, actually, I think it did. It was in favor of -- it was like .68 and the confidence interval went up to .98. So it would seem that the chance that a new study would show that it included 2.0 is very remote, and so you wouldn't have equipoise for your hypothesis, for your null hypothesis at all.

So I want you to comment on that.

DR. BONUCCELLI: So what you're picking up on is that I do believe we have a considerable confidence of an expectation that our relative risk will be less than 1, based on the data that we do have.

However, we do need to acknowledge that that was not from a single randomized controlled trial, where we had the U.S. device -- for example, we use Turbuhaler outside of the U.S. and that included Turbuhaler information, because we consider safety questions -- the safety data to be relevant from all of our data.

So I think the opportunity we see here is an opportunity to try to address the question in a way that is more acceptable to the scientific community in that it comes from a randomized trial.

Your other point is about whether it's ethical. I think Dr. Andersson did actually raise that question. Our original question was can we justify studying this again and, in particular, can we justify taking people to an ICS alone arm when we know an ICS/LABA treatment is better.

The way that that has been justified in the past is twofold. One is to explain this is a regulatory question that we are trying to address and there are ways to adequately address the needs of those patients, less convenient perhaps, but there are

treatments that can be added during the course of the trial that would allow us to say that it's ethical to conduct.

DR. SCHOENFELD: I don't have any trouble with the ethics. I guess the question, which I think you've tried to answer, is whether, in fact, there is an issue about the hospitalizations. And that's sort of the question, because I don't know if you -- you didn't show the individual trials, whether the individual trials were big enough to exclude 2, but at least the meta-analysis robustly excluded 2.

DR. BONUCCELLI: I think Dr. Carroll wants to add something here.

MR. CARROLL: Thank you for the question. In the meta-analysis that we did that you're referring to that we displayed in 2008, each individual trial by itself would have a relatively wide confidence limit, as you saw.

The whole purpose of the analysis that the FDA required was to gather together data that were from consistent, randomized, double-blind, placebo-controlled trials. So that overall, when we put those

data together, we can provide the best possible estimate of whether there is or is not increased risk.

What we found is, exactly as you say, that the relative risk was .62, with an upper limit that excluded 1. So that data would be suggesting, based on that aggregation of data, that the risk is most likely less than 1, based on that meta-analysis.

DR. SWENSON: Dr. Platts-Mills?

DR. PLATTS-MILLS: Thank you. I would like clarification from both companies about the Salpeter data, because both companies have said they have trial data showing that ICS plus LABA produced better control, less acute events, and both companies deny that there were any deaths during trials of combination treatment.

So if we go to figure 2 of the Salpeter analysis, in part 2, which is concomitant corticosteroids, there are 14 events. Are the companies saying categorically that none of those were deaths?

DR. BONUCCELLI: Hang on just a second. I'll see who would have the answer to that question.

Tomas, do you have it?

DR. PLATTS-MILLS: I think we need to hear from GSK that none of the 8 in the pooled trials, the 8 events in the pooled -- were there really 8 events in the pooled trials and were any of them deaths?

DR. ANDERSSON: I can clarify regarding the 3 events that's there from AstraZeneca studies. As Dr. Bonuccelli pointed out, these 3 events are not part of the analysis made for the 2008 FDA analysis, because of the specific requirements set up by the agency.

There was a publication in 2009, with Dr. Sears as the main author, where a much wider database on formoterol trials were published, in about 70,000 patients, I believe, with open trial studies that did not compare LABA to non-LABA and so on, and all of these cases are included in that.

So it's with the strict definitions put up by the agency for 2008, with only double-blind randomized trials comparing LABA to non-LABA, looking at on-treatment period, and with an outlined adjudication process, these events did not qualify.

They are described in the briefing book. The narratives are there. All the death cases are, obviously, included in the all cause mortality, because the cause may be debatable, but dead or not is easier to decide.

DR. KNOBIL: For the GSK trials, most of the trials reported there were not LABA plus ICS as study drug. So in patients who received ICS --

DR. PLATTS-MILLS: I'm sorry. In figure 2, in the second half, it says GSK pooled trials of concomitant corticosteroids, that there 8 eight events with beta-agonists and 3 with corticosteroid alone. Is that correct?

DR. KNOBIL: Well, let me explain what I'm trying to say. So there was a difference in the event rate in patients who received a LABA with background ICS, which means that they reported they were taking it at baseline, but it wasn't a study drug. So in that case, there were more events. The 8 and the 3 are a subset of what I think we reported.

If we look at the patients who received LABA as a study drug and ICS as a study drug in separate

inhalers, there was 1 death and 1 intubation. But if you looked at the studies of Advair, as I mentioned before, there were no deaths and no intubations.

So it's difficult for us to figure out where all these studies came from, but when you looked at study drug, that was the use of the drug was monitored by the study, we had 1 death and 1 intubation.

DR. PLATTS-MILLS: Right. So that if we then go to table 2, in the subgroup analysis, at the bottom, it has asthma event and then this very scary item, deaths, with an odds ratio of 4.03. This is in table 2 of Salpeter. Is that right?

What we're saying there is that none of those -- that data is not related to combination therapy.

DR. KNOBIL: In a fixed dose combination, that's correct.

DR. PLATTS-MILLS: That's not fixed dose combination.

DR. KNOBIL: That's correct.

DR. PLATTS-MILLS: That's LABA.

DR. KNOBIL: That's correct.

DR. PLATTS-MILLS: Because when you read this paper, you read it through and you get the impression that it's moved over to combination therapy and then you get this table with this really serious death odds ratio, and the truth is it's not related to combination therapy.

DR. BONUCCELLI: Could I also add a clarification? On the AstraZeneca cases, 1 occurred off of treatment, 2 were determined not to be asthma-related deaths. So it's not just that they weren't related to combination therapy, they weren't necessarily all related to asthma.

DR. SWENSON: Dr. Mosholder, you have some comments, I see.

DR. MOSHOLDER: Yes. Just a further clarification about the numerator for the Salpeter paper. The 2 asthma deaths from the AstraZeneca formoterol trials that are in the Salpeter paper, but which were not -- we did not see in the datasets reported to us for the December 2008 advisory committee, actually appear in Dr. Sears' paper from last year, the meta-analysis in table 4, and there are

2 asthma-related deaths listed there, a 65-year-old woman and a 13-year-old boy.

I wonder if those are the deaths that were just referred to as being judged not asthma-related and, therefore, they were excluded from the dataset that FDA got in 2008.

DR. BONUCCELLI: Dr. Sears' analysis was also non-adjudicated events. The 1 death in the 13-year-old was a child who was intubated and died from sepsis, and so, during the adjudication, became a sepsis-related death.

The other one, I believe, was a subarachnoid hemorrhage that was determined later on. There was a time -- after. Dr. Sears can clarify. But I would say that all the cases of death were available to all the advisors for the December 2008 event.

DR. SEARS: Very briefly, because this highlights the point of doing different analyses for different purposes. When we wrote up the full AstraZeneca dataset, our mandate was to look at everything. And so we included all the deaths that the original investigator attributed to asthma.

The boy was later, as we heard, adjudicated as a non-asthma death, died of complications of treating his asthma. We had included it. The 65-year-old actually died a day or two after the treatment was stopped. And so under the FDA rules, that was also excluded. That's why those don't appear in the FDA database analysis, but they are in the ERJ paper that I wrote.

DR. SWENSON: At this point, we'll take our scheduled 15-minute break and resume again at 3:25.

(Whereupon, a recess was taken.)

DR. SWENSON: Welcome back, everyone. We'll now proceed with the presentation by Novartis and we will have, I believe, Dr. Fernandes begin the discussion.

MR. FERNANDES: Committee members, FDA staff, fellow colleagues, and guests, good afternoon. I'm Peter Fernandes from Novartis and on behalf of my colleagues from Novartis and Merck, I thank you for the opportunity to present to you our LABA safety proposal and to discuss with you the key concepts that we have taken into consideration while drafting these

proposals.

Up front, I'm going to let you know that we've made some changes to our clinical proposals and our statistical plans or outlines that you have seen earlier this morning and in your briefing book, and this was done to address recommendations from two very recent FDA documents. And you are familiar with these two documents, the Foradil labeling and the FDA briefing book.

Our initial proposal in pediatrics, which you've seen in our briefing book, which recommended the use of the fixed dose combination was based on conclusions from the FDA's joint advisory committee meeting, which was held last year, where it was clearly pointed out that the greatest need for additional safety information was in the most vulnerable population, that's pediatrics and adolescent, and, if I quoted right, also, had the African-Americans in that.

During my presentation, I will also briefly outline the risk mitigation strategies that we have incorporated, as well as highlight key proposed

labeling changes, that I understand is not the topic of discussion today, but I will present a few of these concepts, as we believe that they may influence the way you conduct future clinical studies.

To begin, I'll give you a very brief history of Foradil. As you see, Foradil was first approved in Europe and in France in the '90s and, almost a decade later, in the U.S. In Europe, it's approved for two doses, the 12 and the 24 micrograms, while, you see, in the U.S., it's just the 12 micrograms.

It's approved in asthma for all three subpopulations, pediatrics, adolescent, and the adults. It is also approved for exercise-induced bronchospasm and COPD.

We believe Foradil provides a unique benefit to the clinician, allowing flexibility to adjust doses independent of the LABA dose for certain patients. And as you know, previous advisory committee meetings and ongoing safety assessments are changing the way we look at LABAs.

So following the last advisory committee meeting, we initiated activities to better understand

and communicate the potential risks of LABAs in patients with asthma. In February 2009, we submitted a labeling amendment and a revised medication guide, that you can also refer to as the REMS, to the FDA and we're working with the FDA right now to finalize these documents.

We propose additional educational and risk mitigation strategies and these were done specifically to highlight the need for concomitant ICS use with LABAs and to address the potential risks associated with LABA use.

Now, why are we here today? To put it very simply, it's to design a safety study. FDA requested sometime towards the latter part of last year that the sponsors of LABA-containing products -- and I understand LABA-containing products that are approved in asthma -- to submit a proposal for a safety study.

We also met with the FDA a little before Thanksgiving and got quite a bit of feedback and information as to what is needed to be able to come up with these proposals.

We understood that these study designs that

we should provide should be relevant to the current treatment recommendations, and, by that, I understand they are the current NHLBI 2007 guidelines, which talk about the stepwise approach for managing asthma long term in adults, adolescent, and children, and the current approved labeling. If the recommendations have changed, I think it would be important that we are aware of that.

Study design should also be adequately powered for a clinically meaningful assessment of risk; that is, choosing appropriate endpoints to address the issue of relevance and concern and assigning an acceptable level of risk that is meaningful.

I'm not going to go into anymore details on these two points, because our next speaker, Dr. Pascoe, will very clearly address these two points.

The last point, able to be completed in a timely manner, our understanding is somewhere between 5 to 10 years is the estimate that we have put forward. And the hypothesis to be tested, again, I'm not going to repeat this, because I think you've heard

it at least 8 to 10 times today.

But the assumption in order to prove or test this hypothesis, we believe, would require that the patients be maintained on LABAs throughout the study duration. To test this hypothesis, stepping down from LABAs during the study will not allow this hypothesis to be tested.

Now, we received, on February 18th, proposed labeling changes from FDA. And I understand that the scope of today's meeting is not to discuss the relevance of these labeling changes, but I have identified three points which I think Cathy, too, had highlighted a little earlier, which we need to take into account when we deliberate and discuss potential protocol outlines.

The first is the use of a fixed dose combination. Here, we will need to consider whether the study groups, which is the adolescent and the pediatrics, should be put on a fixed dose combination relevance over the free dose combination is also applicable.

The second is LABAs should be discontinued

once asthma control is achieved. This could be interpreted as LABA step-down from any NHLBI guidelines, which is step 3 to 5 and I think maybe even 6, as this could limit any long-term safety studies of LABA and in ICS.

Here, an option to consider is potentially maybe reducing the study duration to 3 or maybe 6 months. And the last is LABAs are not recommended for patients whose asthma is inadequately controlled on low to medium dose. In this case, LABAs may need to be conducted -- studies may need to be conducted in a more severe group of asthmatic patients.

With this, we also have several of our clinical experts and consultants who are also here to answer questions after we finish our presentation, but I will now hand over to Dr. Pascoe, who will give you the clinical proposal and protocols.

Thank you.

MR. PASCOE: Thank you, Peter. Good afternoon. Novartis are very enthusiastic that we make progress in this area. We recognize that from the patient and prescriber point of view, there is a

lack of clarity, which is beholden on those of us in this room to try and provide some answers to.

We believe that this conversation can be taken forward by an assessment of risk-benefit and any studies we want to provide to address that need to have the ability to impact clinical practice.

So I thought it would be useful just to look at some concepts around what these studies might deliver and to remind ourselves of what we can actually know from clinical studies. It is clear that for drugs that do not positively affect an outcome, you can never exclude a negative effect.

All you can do is exclude a risk above that level and in order to do that, you have to design a study aimed at that risk. And from our perspective, the critical component that we have to decide in the next two days is what is that level of risk to be excluded.

Just to briefly look back over recent history, we've seen, in the mortality arena, around the question of LABAs and a background of ICS, a number of excellent meta-analyses and the numbers I've

got here reflect the numbers of fatalities recorded in those studies.

One of the confusing things is that we are used to looking at series of studies and coming to decisions on the cumulative value of them. In this arena, however, as Professor Sears pointed out, the meta-analyses replicate the same data.

So the fact we have had a significant number of analyses providing similar answers reflects that the data is similar, and, clearly, you can look at these studies and see formoterol and salmeterol must reflect different cases.

But to my math, and it's difficult, to be sure, this entirety of data reflects 4 fatalities. And that, for me, is a sobering thought, when I've heard people with real clarity over how to interpret this data.

I think it does ask a very real question and I think it does give us pause for thought of how we can clarify whether or not this risk is real; as I said, more importantly, what level of risk we can exclude.

When we come to hospitalizations, we believe the data is clearer. We believe that when we look at six meta-analyses, and these are, I think, all the significant meta-analyses, and we've chosen to exclude sponsor analyses. However, I think some of the analyses done by my colleagues at GSK and AZ are actually very informative.

Now, these first five studies look at ratios, either risk ratios or odds ratios, and the last study, performed by Dr. Levenson, looks at risk difference. And I would argue, when you look at that data, the only studies through different -- again, it's similar data, but the methodologies have suggested that the effect of LABAs on ICS is, indeed, protective.

Well, indeed, there are four studies which don't show a protective effect, but the estimate is close to unity. In the last study, where risk difference is looked at, and this is risk difference per 1,000 patients, which is probably the most, certainly, from our perspective, pessimistic of the studies, I think what's important is to try to

quantify that data in terms of the impact it has on the patient.

We are saying here, for the point estimate of .25 per 4,000 patients, that relates to 1 hospitalization event per 1,000 years. And to be a little trite about it, that means if you started taking your long-acting beta-agonist a millennium ago, you would have had daily benefit for an average risk of 1 hospitalization.

Now, if you take the worst case scenario from this data, with the upper end of the confidence interval, that's working out at less than 1 hospitalization per 100 patient years. So from our perspective, this data does indicate that this question is answered within the boundaries I set at the beginning of can you justify the non-excludable risk in terms of giving the therapy.

The only question mark, I think, that remains over these types of data is that they're not provided in a single randomized controlled study. And I think where we would be very concerned about that is if the methodology for identifying and collecting the

cases was dramatically different.

But given most of these studies are being conducted by industry, the method by which hospitalization is recorded is rigorously defined and it is mandatory that these events are recorded.

From our perspective, we do not see that as a concern that weighs up against the potential error in the studies. So there is some room for doubt, but I think we have to always say how much doubt can we tolerate.

So what are our key conclusions? Well, I think, like everyone else here, we agree that LABA use in the absence of an ICS is not appropriate, and the guidelines and labeling currently reflect that.

I think, as I've just mentioned, further studies on asthma-related hospitalization are unlikely to change the risk-benefit, because the risk-benefit has been shown to be positive. And the signal, if you believe one exists, and I'm not sure there is a strong signal there, the worst estimates from the evidence, I think, are justified in terms of the clear benefits that we all believe LABAs bring.

Around the question of mortality, this is clearly of concern and it is our perspective that for similar reasons that GSK and AZ have indicated, that randomized controlled studies will not help us answer this question. And I think we heard a very good statement earlier on about deciding what level of risk to exclude before you can exclude that the study isn't feasible, and I think that that's absolutely right.

But our conclusion is based on an assessment of a level of risk which we think would be helpful to exclude. And by helpful, I mean not only if you see a study where there is a risk beyond that level and you say the risk-benefit is broken, but the very important question, which has driven all of these meetings, is when you see an estimate below that level, but it's to clearly significant, people don't accept it's clearly true, and that continues to impact our labeling and our behaviors.

So to address the question, you have to address both sides of what does the data mean if it falls either way.

So Novartis has said what we shouldn't be

doing. And what do we actually think we can do to help? And I think that's probably, in some ways, a more important question.

Well, following the last advisory committee, there were a number of areas of concern identified where more data would be helpful. And you can see here that of these four areas, it's our belief that pediatrics, since that time, the efficacy side, which was an important part of the debate, has been addressed in some really very good studies and the efficacy benefits of LABAs have been clarified.

Furthermore, I think the risks we saw in those analyses have not been borne out by the data on the fixed dose combinations. But nevertheless, the fact that the agency has suggested pediatrics for further studies has left us to focus on other areas.

We believe an area that is actually even less well represented is adolescents, and we think this could be a fruitful area where we could add some knowledge to the conversation and bring forward a better understanding of the risk-benefit.

In terms of African-Americans, we believe an

individual study there is going to be problematic and an approach of taking data from each of the potential studies and bringing that together to get a better assessment may well be valid, and we would contribute a significant number of African-American patients from our adolescent study towards that end.

But as pointed out earlier on, I don't think it would be possible to utilize that data in that subgroup from that one study as a standalone debate. And we would commit to studying polymorphisms in this patient population.

So what does our study actually look like? Well, it's a very simple study design, where we would add Foradil to a moderate dose of ICS against the same moderate dose of ICS on its own. And we left the duration vague, because it clearly was going to be a significant topic of conversation, but we think the study would probably have to be between 6 and 12 months.

In terms of the sample size, assuming it was 12 months long, it would be just over 3,000 patients in the study. And here is the important part. What

risk difference do we want to exclude? And our suggestion is that a risk difference of 1 percent is a level of hospitalizations which you could feel comfortable that the benefits outweighed the risks.

I know I will be asked why 1 percent, not 1.5 or .5, and we have to accept these things are arbitrary. In order to take the debate forward, we have to decide and it occurred to us that a risk difference of 1 percent, with a very optimistic assessment of longevity, roughly equates to one event in a lifetime of asthma, and that seems somehow an appropriate way to communicate to patients and doctors.

So that is our suggestion. We know it will be debated. The population of interest is adolescents, as we stated, and they would be uncontrolled, on a moderate dose of ICS or at the lower end of the moderate dose of ICS.

The study conduct here is extremely problematic, because we've heard what the problems are of not allowing rescue therapy. And we've had suggestions that for 3 months, you can maintain people

on a moderate dose of ICS.

It is our belief that the patients who would need a step-up in therapy, if that is not allowed and they leave the study, we always think a 10 percent dropout rate is problematic. But if we believe the very patients who are going to provide the information on the endpoint of interest are those patients whose asthma worsens, to allow them to leave the study is disastrous if the dropout is differential.

So we would advocate that you have to increase their inhaled corticosteroid dose under a specified regime and under pre-specified conditions, and that allows a decision to be made if the frequency of that is similar between the arms.

As soon as we see that differs between the arms, analysis struggles to help us interpret that and I think that's a weakness of any of these studies, which is extremely difficult to get around and it is a significant problem.

So what endpoints would we study? Well, we've rather avoided the debate here by putting intubation and death in brackets and I think it sits

between the pediatric proposal and the adult proposal. And our view is the frequency of those events would be so low, whether they're included in the primary endpoint or included in a subset listing actually probably isn't terribly impactful.

The secondary endpoints, this is a collection of endpoints that we're all used to in asthma studies, but I think why this is so important is we have become polarized into a debate about risk-benefit, around hospitalization, and we seem to have a pendulum on which you can swing across this.

But as was pointed out earlier, for most of these patients, asthma is a day-to-day disease, where hospitalization is a very unlikely event. We're all talking about background rates of 1 event per 100 patient years.

So in terms of assessing risk-benefit, we should not marry up just hospitalization. We have to weigh out the negative side, if, indeed, there is one, but we have to have an assessment of the potential benefit in terms of a very serious disease.

We're talking about a population of patients

here who aren't patients who occasionally take albuterol. We're talking about people who have earned a high level of maintenance therapy and are still symptomatic.

As was said, our underlying background assumption, our rate of the underlying assumption is 1 percent, and I'm sure there will be some debate around that. We feel that the change in hospitalization rates over the past 15 years has been significant and some of the data we've seen presented overestimates the rate.

I can tell you that we're conducting a study at the moment looking at hospitalization rates and we've just had over 200 patient years of experience and had our first event. So I think the 1 percent, if anything, is giving us a higher rate than we believe we will see in practice.

So just graphically to demonstrate the study regime -- and I hope my explanation was sufficient to convey that. In looking at our sample size estimates, I alluded to the fact we were interested in risk difference and I alluded to the fact that risk

difference is important to patients, because they are interested in what number of events they are likely to expect because of the therapy.

But there are a couple of interesting things that happen with the mathematics of risk difference. One is to achieve a similar answer to a ratio approach, you actually need a slightly smaller number of patients. The other is that as the event rate drops, you're able to detect bigger differences for the same sample size.

One of the problems with non-inferiority studies is people are able to mentally swap between the upper boundary and the point estimate. And just to be clear, when we exclude a rate of 1 percent, that means the top end of the confidence interval will be less than that.

But what I've illustrated here, in the middle column, I've listed differences and some examples of how this study would turn out, is what would be the point estimate for the difference.

So if, for example, in the highlighted in blue, we see our 30 events, a split of anything worse

than 17/13 would indicate we haven't met our previous failure criteria.

Back to one of my original points of we need to try contributing new knowledge to these questions. When we look at adolescents and we look at Levenson's estimates of the risk there, and I think this probably remains the best effort to look at adolescents, we can see the confidence interval around the risk. The upper end was 1 percent, but that wasn't annualized. So the annualized rate there was 2 percent.

So if our study excludes a 1 percent risk difference, we will be significantly impacting the assessment of risk difference in this patient population.

Now, on to the operational complexities of running these very large studies, very briefly, studies you're all familiar with. You can see that in this arena, the majority of adult studies, which are the top three studies, recruit at approximately 3 to 4,000 patients per year. We believe, in adolescents, this would be more likely to be 1,000 patients per year.

Therefore, to recruit 3,000 patients would take over 3 years. And here is an area of concern for us. If we take these individual studies in isolation, when we see these delivery times that I think AZ and GSK have delivered, they're all dependent on being the only study. But our belief is internal capacity within our organizations is not the rate-limiting step. It's the external capacity.

We are further concerned that when studies go on for many years, the ability to sustain enrollment at the original rate is highly questionable. So these figures, I think they've been offered by all the companies, are an upper end of what you can achieve if you're the only study out there and you've got a reasonably short duration and your study question is of interest.

Some discussion points on study design. Clearly, whether or not we're taking asymptomatic versus asymptomatic patients is crucial, because the search for symptomatic patients makes the study harder to recruit. But we believe you cannot enroll asymptomatic patients into a step-up study design.

You cannot ask people who are well controlled to take more medicine to ask a question of interest.

As we've said earlier, if we use symptomatic patients, they would need to have step-up therapy built into the study either on a rescue basis or on a mandated basis, and that will induce potential bias into the study.

If we look at the comparison of the same dose of ICS or an increased dose, this is a subtlety here that is crucially important. If you compare a LABA plus ICS to an increased dose of ICS, you are not asking the question, what is the safety profile of a LABA. You are asking a question about comparative regimes.

It might be that's the question you want to ask, but I would urge everyone to recognize that you have to identify the question and design the study appropriately to bring the answer home. And the reason that's important is the efficacy component of the study with increased steroid dose then becomes very much a part of the balance.

In terms of duration, I think it's been

touched upon by many other people today and, clearly, longer means shorter, shorter means longer. So I won't talk about that.

So as far as specific operations, very quickly, just to give you an example, to run the study would take 5.5 years, we believe. If you decrease the dosing period, you will increase the duration by 3 and 6 years, respectively, and, as we've said, the study would be dramatically impacted if it competes with other studies.

So in summary, Novartis believe that large randomized clinical control trials are very unlikely to provide data which will help us move prescribing practice in terms of our assessment of risk-benefit.

Any excess risk or mortality that is meaningful is also not addressable in a randomized controlled study. Novartis proposes that we would study adolescents to significantly change the assessment of risk-benefit in that group.

Thank you.

DR. SWENSON: Well, thank you. We now are magically ahead of schedule. So there will be

considerable time here for questions. And we'll start with our list here. I think Dr. Fink is the top of the list here.

DR. FINK: Yes. I had a question, actually, I think, to all three companies in terms of ethics and equipoise, which is in their data they have presented to date, what is the inclusion of African-Americans and at least Caribbean-Hispanics, because if those populations are underrepresented, but at higher risk, then there is a greater degree of ethics and equipoise to the proposed studies.

Secondly, specifically to Novartis, because of the complication of what they're presenting, where alteration of steroid dosage would make the study hard to interpret, how will they deal with the difference that their study potentially allows multiple different steroids at not necessarily clinically equivalent or biologically equivalent doses to be used, unless they go to a fixed steroid for all patients in their study?

DR. SWENSON: Okay. Well, I'll ask Novartis to handle both those questions when their turn comes up, but I think we have AstraZeneca here to kick off.

DR. ANDERSSON: I can address the question of African-Americans in the Symbicort studies. In the studies that provided the background for the approval in the U.S., there were about 10 to 15 percent of African-Americans in that study sample, and the risk profile and tolerability was similar in the African-Americans to the total population.

In addition to that, we're recently just finishing up two studies, one 3-month efficacy study and one 1-year safety study in 700 patients, African-Americans, comparing Symbicort to the corresponding dose of budesonide.

So that will add to the data. It's not available yet, but it will add to the data we have.

DR. KNOBIL: Yes. One of the reasons why there's a lot of questions about outcomes in African-Americans is because of the results that we saw in SMART.

In SMART, as you heard already, it was a 26,000-patient study, approximately 18 percent of the patients in that study were African-Americans. And it appeared that African-Americans had worse outcomes on

salmeterol.

I think it's important to realize, though, that even at baseline, the level of asthma control in the African-American population was less -- less well controlled than in the Caucasian population. There was also less use of inhaled corticosteroids. Only about 38 percent of African-Americans were using inhaled corticosteroids, whereas about nearly 50 percent were overall.

So in order to answer that question, GlaxoSmithKline did do an African-American-only safety study. If you could show the slide, please. We did show this at the last advisory committee. And as you can see, it was as study of about 500 patients, all African-Americans, looking at the impact of comparing Advair to FP alone. In this case, it was Advair 150 to FP 100.

As you can see here, there was no increased risk in exacerbations. In fact, numerically, it was a little bit smaller, but it wasn't necessarily powered to show a difference between the arms.

I think it's also important to note that in

that study, there were two hospitalizations in the Advair group and there were three hospitalizations in the FP alone group.

The bottom part of the table shows all of the African-Americans that were represented in our database. So in each individual trial, typically, the number of African-Americans is low.

So what we did is we put all of the data together from all of our trials to get a better idea and what you see here is that the number of asthma-related hospitalizations was equal in those receiving Advair versus those receiving ICS alone.

So, again, doing a trial with an adequate number of African-Americans to have a powered study is going to be difficult. So, for example, the trial at the top took 13 or 14 months to enroll 500 patients. So it is more difficult, but it's something that we can look at as a subset if a large trial is done.

MR. PASCOE: So two questions. The question of the steroid dose, just to be clear, we're proposing that subjects are randomized to the same steroid and the same dose to start the study and the analysis

would be done on intention to treat.

However, recent data does suggest that after 3 to 6 months in this type of study, we will see as many as 50 percent of patients poorly controlled. So the correct methodology, and I'm not suggesting this, would be to drive those patients through the study, not change their medication, and see how many of them are hospitalized.

The only method we can actually use is to somehow either let them leave the study when they're poorly controlled, and, therefore, they will be treated in an ad hoc fashion by their physicians and won't be potentially lost to follow-up, or, alternatively, we mandate when and how they are handled.

Then, as I say, if that breaks evenly, you don't have a problem to deal with. If it doesn't, then you'll have to make an assessment of how significant you think that difference is.

To the African-American question, I think it's very much in line with our thinking, is that large studies in the general adult population are

really not going to add much value here. But if there are specific subsets where either there is a suggestion of excess risk or there is insufficient data to quantify the risk, because they're the same, these are the subsets we should be studying.

Now, we've chosen to address one today, but I think you could equally argue need in African-Americans and I think that that would be the feasibility of such. We haven't gone into it in the same detail, but I think in terms of addressing a global study and maybe a higher risk difference because of the uncertainty, that would be a possibility and it would be a valuable thing to do, in our opinion.

DR. SWENSON: Dr. Ownby?

DR. OWNBY: I had a question that no one has addressed yet that our patients always come in with, and that is the question of what are all the risks; not just the risk of sudden death or an intubation, but the risk from using higher doses of inhaled corticosteroids or the steroid effects.

Growth suppression is the one that a lot of

parents ask about. But I'm aware of some reports of cushingoid appearance from individuals on topical corticosteroids and I don't know what the prevalence of that has been in any of the studies, whether it really shows up or not, and I'm surprised that no one has mentioned that.

DR. SWENSON: I think Dr. Krishnan might have an immediate answer to that.

DR. KRISHNAN: It's a separate question.

DR. SWENSON: Okay. Anybody willing to address that question? Okay.

MR. PASCOE: I'll take a stab first, if I may. So I think it raises a really intriguing point. The first point is the question here is not whether or not to use LABAs. It's a question of whether to use LABAs and something else. So in terms of the manifest safety of the alternatives, I think that should be rolled into our assessment of risk-benefit.

In terms of your specific question, I think any study of this magnitude, even the 3,000 patients we are suggesting, would look at those risks and have full facility to quantify them.

DR. SWENSON: Just for the record, I would like to ask you to just state your name before you answer the question.

DR. KNOBIL: Kate Knobil, GSK. Just to specifically answer the question of how often we see it, generally, we don't see cushingoid appearance in our studies. The doses of fluticasone propionate, either by itself or in Advair with a LABA, generally have very low systemic exposure, because most of the drug is cleared by first pass metabolism.

However, that is not to say that if you take very, very high doses, above the labeled recommendations, you could get a level of exposure that could give you at kind of effect.

Now, in children, the only dose that is approved in the United States is Advair 100 twice daily or FP 100 twice daily. So anything above that could potentially cause growth suppression, although in the studies that we've done, the level of growth suppression is small, approximately 1 centimeter, and there appears to be catch-up growth.

You do bring up a very good point, though,

that if you push inhaled corticosteroids in order to avoid using a long-acting beta-agonist, you could have some of these effects that you wouldn't necessarily see at the normally used or labeled doses.

DR. SWENSON: I have some questions for Novartis and AstraZeneca to just clarify their proposed study design. For AstraZeneca, on your slide CD-6, where you have the schema of the study, I just wanted to ask you about the bulleted statement that open label add-on of additional asthma controller medication would be allowed.

Could you just clarify whether -- I presume that would include inhaled corticosteroids and whether you would allow that in both arms and that that would be a measure of efficacy or failure of efficacy, if it's added on.

DR. ANDERSSON: Okay. Thank you.

DR. SWENSON: This is Dr. Andersson.

DR. ANDERSSON: Tomas Andersson, AstraZeneca. Yes. The reason why we proposed to include it is, obviously, as we heard before, putting patients on ICS or ICS/LABA and hoping to keep them in

a study for up to a year will inevitably lead to more failures in the budesonide arm, because it does not control asthma as well as the combination treatment.

So either you just keep that and patients drop out and are put on other medications and either you don't look at it at all or you do full-time follow-up, but then you study them where part of the time they are on another treatment, not the study treatment.

The alternative to that or to mitigate that, we propose to -- the randomized treatment will be blinded. So patients don't know what they were on. But to keep patients in the study, we would propose to allow open label add-on of ICS, also, during the course of the trial in order to keep patients in.

It's a tradeoff and it's a compromise, but in our judgment, it's a better way to retain patients and keep them in there than to lose the worst controlled patients and then not being able to study them properly at all.

DR. KRAMER: You track that as an outcome, their need for the additional --

DR. ANDERSSON: It's one of our proposed secondary outcomes, because, obviously, it's a measure of treatment failure.

DR. KRAMER: Also, could I ask the other question for Novartis? Actually, it's two things. One is you had in your schema, but didn't address it -- let me get the slide. It is slide CO-9, you had a low dose ICS run-in, and I just wondered if you could explain how that will target the right patient population if you have to have a 2-week run-in on low dose ICS.

Do you want me to ask you the other question so you can answer them both at once? The other question is in the December conversation, December 2008 advisory committee, there's a lot of concern when you give single-agent LABA, even if you say the patient should be also taking inhaled corticosteroid, of the impact of non-adherence.

Since your study is the only one that's actually looking at a separate LABA and ICS, I just wondered if you were planning on assessing adherence or some measure of whether or not there was compliance

to both agents.

MR. PASCOE: Steve Pascoe, Novartis. I think to the first question, experience shows that if you bring patients into asthma studies who are apparently poorly controlled on a set dose of steroids, that once they enter the study, you get a high level of control. So it is actually a compliance issue.

So one way to mitigate against this is you place them in the study on the dose at which they're apparently poorly controlled and if they remain poorly controlled after the run-in, they then get randomized into the study.

The other question relating to compliance, I think it would be critical to ensure compliance, monitor compliance, and be able to assess it at the study end. And to that end, our choice of steroid may well be guided by our ability to find compatible electronic monitoring devices that record date and time of administration and patients who were noncompliant in the study would be taken out of the study.

DR. SWENSON: Dr. Fleming?

DR. FLEMING: I'd like to go back and just revisit some of the context for -- it was mainly in the AZ presentation. I was raising some issues earlier today in the GSK presentation about whether the margins were too small, particularly for the most serious events, making the case that if we're getting global benefit to patients, that even as serious and as important as an asthma-related death or intubation would be, requiring that we rule out that there even be 1 per 100,000 or per 10,000 people may be overly rigorous.

I was arguing that you could -- and we'll discuss this more tomorrow -- you could justify a larger margin, allowing to have up to a doubling or a tripling, but ruling out something in excess of that in the context of the importance of the benefit.

I had made a quick comment, though, that it seemed that their margin that they had put forward for the asthma-related hospitalization made sense. It was a 1.3, in that context, basically ruling out 50 excess events.

My concern is, at least as I understand the AstraZeneca, they have now gone in the opposite direction of saying you can have up to a doubling, meaning that you could allow up to 200 additional events per 10,000 person years before it's really clinically unacceptable and, by the way, that conclusion would still be achieved even if you had 64 excess events.

Now, they put forward very appropriate criteria when you design a trial. You want it to be ethical, relevant, and feasible. And, in fact, if you rule out a doubling, that's relevant, but the question is, is it adequately informative, is it adequately relevant, and this isn't novel.

We've gone through these discussions of margins in other disease areas. I'll just give one example. In Type II diabetes, in essence, in that setting, what has been required is ruling out a 1.3 margin on cardiovascular deaths, stroke, and MI.

One could say, "Well, what if we just rule out a doubling in asthma-related hospitalization, is that relevant?" Sure, it's relevant, but it doesn't

answer whether you're ruling out excesses that are smaller than a doubling on that endpoint and, furthermore, it doesn't at all address whether you're ruling out what we most care about. In that setting, it's the cardiovascular death, stroke, and MI.

So in this setting, and we'll discuss this a lot tomorrow, where we set that margin is always benefit-to-risk. How important is the benefit? And I am persuaded there is important benefit and, therefore, it is acceptable to have some excess risk.

But it seemed to me that the GSK presentation, while being overly conservative for what would be acceptable in excess risk for asthma-related death and intubation, seemed appropriate for hospitalization. The AstraZeneca is going to almost a fourfold more lenient approach.

So it's confusing how this justification is that if you have a 2 percent background rate, meaning 200 events per 10,000 person years, it's okay to have up to 200 extra events. Actually, what I'd be hoping is that I'd be reducing these kinds of things.

I'm hoping that these interventions, given

to people at serious risk, would actually be reducing things like important hospitalizations that are asthma-related.

So I'm really perplexed as to how, and that's how, of course, you got the small sample size, how we could justify such a large margin.

I'll just make one last comment before your answer. The advantage of being more rigorous in the whole overall population is that if you're designing it, as GSK said, ruling out an excess of 50 percent or an excess of 1.3, a 30 percent relative increase, it does allow you, in the subgroups, like the African-Americans, who are 1/7th of the population, to, at least in that subgroup, have something that's interpretable, that, in essence, allows you to at least rule out a doubling in that subgroup.

So by being more rigorous overall, it actually puts us into a position where we can get something that's interpretable at least in the subgroups.

DR. BONUCCELLI: So thank you, Dr. Fleming. Cathy Bonuccelli, AstraZeneca. First, I just want to

say we acknowledge this is one of the hardest questions being asked to the advisors and we understand that we are here to discuss it. So that's the first thing I would say.

The second thing is, as you pointed out earlier today and as we would agree with, we measure relative risks for a specific reason, and that is to inform decisions on therapeutic choice at the patient/physician dialogue.

So really the question is in that context and in that context, you have to remember, setting a risk to exclude is not saying what's acceptable or unacceptable. It's saying what will we learn from the trial, setting the confidence interval.

So you will get a point estimate --

DR. FLEMING: By the way, just on that point -- I want you to continue, but just on that point, I think as the FDA clearly said, that margin, though, needs to be low enough such that anything less than that is acceptable.

So it's not sufficient to say a doubling is unacceptable, that can be our margin. What's implicit

when you use a margin of a doubling is that anything that's an increase less than a doubling is acceptable in the context of benefit.

DR. BONUCCELLI: Okay. So I'm just going to run through the logic again. Just for the purpose of the conversation, I'm agreeing with you, largely. You're going to get a point estimate and, for the purposes of that dialogue, that will be the most likely estimate.

Then there will be a confidence interval around that estimate that will be the part that you want to decide how confident do we need to be. So that's a clinical question, as you pointed out, and up for conversation.

We have shown, and you've agreed that we've shown substantial benefit. The other point that I think we wanted to make sure people understood is the other tradeoff being made here is how much additional information you can get for the amount of additional investment of time.

So when that tradeoff is made, if 2 is too high, from a clinical perspective, and you want to

drive it down or need to drive it down, that's the conversation to have, it should be had with the recognition of how much additional information will you get for the purpose of that discussion and at what cost. And in these terms, the cost is really a time cost.

So for a sevenfold larger study, three times as long to twice as long, I think, you will get additional information. You will be able to discriminate between 2 in 100 versus 3 in 100 events. Instead, you'll be able to discriminate between 2 in 100 versus 2.5 in 100.

DR. FLEMING: Well, let me be more specific on that, because the argument that at least you seem to be making is for sevenfold additional information, you're not getting that much more precision.

I would strongly disagree. You get considerably different precision. So if you have, in fact, a 2 percent annual rate in the control, which is 200 events per 10,000 person years, if, in fact, you're trying to rule out a doubling, which you can do with 1/7th the sample size, when you're done, you're

going to declare a victory if you have an estimated 64 excess events, with the possibility you could have an extra 200, on an endpoint that actually I would have thought maybe we would have hoped we could have had a positive effect on.

Whereas, for sevenfold the information, what you'd be ruling out is something that, in other disease settings, seems consistent with what we've tried to do, ruling out 60 excess events, not declaring victory unless you have any more than 22 excess events.

Those are very different sets of confidence that you're going to have. If the background rate is 200, can I rule out 200 excess events or 60? Those are profoundly different in terms of insight and reliability.

DR. BONUCCELLI: That's the conversation the advisors will have. I think Dr. Carroll is going to clarify. The other point that you made is that our expectation should be that this endpoint would be improved and that the relative risk would be lower than 1. So I think that was also part of

AstraZeneca's consideration.

Dr. Carroll, do you have a further clarification?

MR. CARROLL: Thank you, Cathy. Of course, Professor Fleming, we agree that we have to be very cognizant of the benefit when setting that margin.

If I could just show you this slide that we have -- see if it comes up -- because I just want to be really careful for the committee and very precise about exactly what we're doing, because I'm not absolutely certain I agree with the excesses that you were quoting there.

What I tried to demonstrate on this slide, and maybe I didn't stay on it long enough in the presentation, is that when we design the study to rule out a relative risk of 2, and we've heard Cathy say that that is, of course, an issue that's going to be discussed, of course, at length tomorrow, but just for clarity, when we do that, then what you find is that the highest event rate on ICS/LABA that can be tolerated and still rule out a relative risk of 2 is on the slide.

It's 2.23 percent versus 1.3 percent. So that gives you an upper confidence limit of 1.32 percent. So it is not the case -- it is not the case that in ruling out a relative risk of 2, that you're allowing the incidence rate to double, not the case.

The maximum increase would be 1.3 percent in terms of the upper confidence limit. And, of course, if we have a slightly better relative risk than 1, then we can rule out a .5 difference. That's the bottom bar and the number on the right-hand side.

So if you look at that and translate the top and the bottom on this slide, what you're dealing with is, in the 4,400 trial, if we rule out relative risk of 2, then you're talking about -- per 1,000 patients, you're talking about an excess of about 10 or 13 events per 1,000 patients, not 20, for example.

Then if you want to drive that lower, if that's unacceptable and you want to drive that lower, you say, no, an excess of 10 or 13 events per 1,000 is too high, if you want to drive it lower and you want to go for a much bigger trial size, then what the slide is telling you is that then you'll be ruling out

not 13 per 1,000, but something like 5 or 6 per 1,000.

There, the numbers are relevant to the design that we have put forward. I hope that's a helpful clarification.

DR. FLEMING: So, Kevin, let me just respond, because I think I'm referring to the same numbers you are. So let's look at this top scenario.

[Laughter.]

DR. FLEMING: So I was working off of your assumption of a 2 percent background rate. And so if you're ruling out a doubling, that would translate to ruling out 200 excess events.

MR. CARROLL: That's not correct.

DR. FLEMING: If you have a background rate of 200 hospitalizations, a 2 percent annual event rate. So if you have a 2 percent annual event rate in the control, then a doubling would be essentially increasing it from 2 to 4.

MR. CARROLL: Yes. That's true, because 2 times 2 is 4. So that's, obviously, correct.

[Laughter.]

DR. FLEMING: See, we're getting to

agreement quickly here.

MR. CARROLL: I'm not going to debate that. But what I'm trying to say is that in the study that we have designed, it's a 4,400-patient trial, relative risk of 2, 88 events. That's what it is.

So you generate your 88 events and if they split 44/44, no excess risk, you're in the middle. That's what you get. I've got this in a different backup slide, but on the top, with the same 88 events, they split out at something in the region of I think it's 53/37, something like that.

DR. FLEMING: So, Kevin, I can be brief here. Let's be brief. Eighty-eight events is correct. So we agree on most of the number. Eighty-eight events is correct if you want to rule out a doubling and the reason you can get that with 4,400 people is a baseline 2 percent event rate, which is 200 per 10,000.

So you're trying to rule out a doubling. That's effectively ruling out an excess of 200 hospitalizations. You win, exactly as you got here, if you're no worse than 1.3. A 30 percent increase

off of 200 is 60. That's what I was mentioning before.

So essentially, as long as your data show no more than a 60 increase from 200 to 260, you'll be able to rule out a doubling. And as you correctly point out, if we actually have an estimate that's the same or if our estimate is positive, then we do a whole lot better than ruling out a doubling.

The risk in doing a small trial, though, is if those of us believe that you need to rule out 1.3, which you will do if you see an estimate of .85, you darn well better be confident that your agent is truly at least .85 or better or you're not going to have a high probability of achieving this.

So what most of us do, as you did, is you're saying, "Well, even though we may think we're at .85, if, in fact, we're the same, we want to have a high chance of success," which is a high chance of seeing no worse than 1.3. That rules out the doubling.

But in simple terms, clinically, if the background rate of the control of ICS alone is 200 events per 10,000, ruling out a doubling is saying I'm

not going to have more than a 200 increase and I win only if I have no more -- exactly as you say -- an estimated 30 percent increase, which, though, is an estimated 60 excess events.

So tomorrow, this is what we need to discuss as to what is the appropriate bar, and there's no magic number here. But that doesn't mean it's arbitrary. And where GSK's calculations were fitting that margin was 1.3.

I was complaining that they did 1.3 even for the rarest events, where I could use a much bigger margin, I believe. But for the common events, as we've done in Type II diabetes, as we've done in OA and RA patients, no, allowing a doubling is almost unprecedented for a common event, because, effectively, it's saying you could have up to -- we're only ruling out an excess of 200 hospitalizations.

MR. CARROLL: I'm going to attempt to have the last word and see if it works out, because I'm sure we'll come back to this tomorrow.

I just want to be really clear about this. The way the study is designed -- and what's really

important here is this top line. And I'm sorry to point the advisors to it again, but it's very important. The way this study is designed is if a relative risk of 2 is ruled out, simultaneously, the upper confidence limit for the risk difference will be 1.32 percent. That's what it will be in this trial.

That means that you have ruled out that the excess is no more than 1.3 percent. So per 1,000 patients, the excess is no more than 13. That's what that study will tell you.

I'd be very happy, Tom, to take you through the math after the meeting, but I guarantee you that is correct.

DR. SWENSON: Mr. Mullins?

MR. MULLINS: Thank you. Two questions. I want to direct my first question to the sponsors, and I have a question, but I want to take the conversation a different direction.

I wanted to know if the sponsors have taken under consideration socioeconomic issues in the way that the patient population behaves. And not all patients, not all of the sample group will behave the

same.

I want to know from the sponsors, how do you capture data from aspects or parts of the population that don't access healthcare in the same way, who use the emergency room for their primary care physician, and who do not have a pulmonologist that they go to regularly?

I think we need to consider that. I want to know from all three sponsors how you address that issue, because, obviously, I think, based on the Bailey study, there are some considerations for subpopulations. I think we have to consider the Bailey study when we think about a 4 percent increase in African-Americans. The occurrence of asthma in children, there's a 4 percent increase of vulnerability among African-American youth.

So I want to take that under consideration and have the sponsors address that.

My second question is directed toward GSK. It's a point of clarification. And that is, it seems that with GSK, there seems to be, obviously, some concern about a randomized study. But with the SMART

study, it was not observational. It was, obviously, randomized, and the initial patient population was 30,000, with 15,000 control arm and -- 15,000 patients in both arms.

Now, it seems you want to double back and go to observational study. And one thing that concerned me is that you said that we would go to -- with observational study, we would be able to go to a pre-selected group of physicians that we've been working with, that would already have patients that they were working with.

I want you to clarify that. That concerns me, because that would exclude a large patient population and prospective participants. And that was one positive thing about the SMART study is you got a cross-section of the American population.

So I would particularly like you to address that question and, obviously, the other three sponsors to address the other concerns.

DR. SWENSON: So, Dr. Knobil, can you take that clarification first, and then the general question? And then we'll have the others follow.

DR. KNOBIL: Yes. So in SMART, it was a randomized controlled trial, but it was sort of part randomized controlled trial and part observational study, as it was one visit. Patients got their study medication and never returned to the site, but were contacted by the CRO that was assisting us with the trial.

There were a little bit over 13,000 patients per group and it did get a cross-section of patients. We did try to assess socioeconomic status in that study, but the only thing that we had at our disposal, because of the limited amount of information that we collected, was zip code and that is a very crude estimate of socioeconomic status.

So based on that assessment, we didn't find any socioeconomic element that helped us better understand the results in SMART. Also, recognize the number of events in SMART was very low and so trying to pick apart whether or not they were influenced by certain factors was limited by the actual --

MR. MULLINS: Don't you think that implies why we need a randomized study, because we are open to

better profiling with a randomized study, because we can look at particular categories and strata?

DR. KNOBIL: Yes. So I'm going to let Dr. Camargo comment further on what the observational study can bring us, because it actually will have potentially more information than we may have in a typical randomized controlled trial.

Just to be clear, we haven't picked a set of investigators that have a certain group of patients. Again, I'll let Dr. Camargo talk about this more, but we're looking at events that have already happened. So it would include all patients in the observational study, not just a certain group of patients in a certain part of the country.

Dr. Camargo?

DR. CAMARGO: I think you raise an important general criticism of randomized trials, and I do want to make clear that I love randomized trials. I do randomized trials. I have publications on randomized trials in recent issues of major allergy journals. I'm on the standing committee of the clinical trial section for the NHLBI. But observational studies have

their role.

So observational studies actually may be better suited at addressing your concerns, because one of the problems with randomized trials is that they tend to enroll patients who are better off, who are better connected, who are different than the general population.

It's well known that people in randomized trials have better outcomes, more adherent, et cetera. In the proposed study, which I reviewed earlier this morning, some of those datasets would include large datasets like Medicaid. I think that would get directly at some of the issues you're talking about. Another one would be the Department of Defense.

There are large datasets with large representation from ethnic minorities and lower income people that we could look at. Part of the planning would be to see if there was sufficient power to do that.

Now, if I accept Dr. Fleming's point about an odds ratio of 4, there would be sufficient power, I think, to look at a lot of these subsets. So I hope

that helps address your concern.

DR. BONUCCELLI: Cathy Bonuccelli, AstraZeneca. You've actually raised a very important point, I think, about the limitations of randomized controlled trials, which is that we generally don't have much socioeconomic data.

The other point that you made is that there are subgroups of individuals that decompensate in asthma and there are those who have a true treatment failure that are addressing their disease on a daily basis and then their treatment fails and they decompensate and go to the emergency room or end up in the hospital.

There are others, and this was talked about in the FDA briefing materials, I believe, the others are those who really are not addressing their asthma and have acute decompensations, sometimes leading to death.

So just to add to that point, I think we have evidence for that in our endpoint discussion about including ED visits. If you look at the ED visits that we would include, we do not quadruple the

number of events by adding ED visits. They're only twice the number. The number only doubles relative to the number of hospitalizations. There's no double counting here.

Dr. Andersson took you through this slide. And what this seems to indicate -- we have Dr. Silverman with us, in the back, who is an emergency physician. What this seems to indicate is that in clinical trials, what you're really measuring is those ED visits that are treatment failure decompensations. So that that population is a different population than the one you've alluded to.

So we would not -- I don't believe we have ideas about how, in a randomized controlled trial, we would capture the population that's not going to be having regular care. These would be patients who have failed treatment. That's the kind of randomized controlled trial population we would have.

MS. ARMSTRONG: Linda Armstrong, Novartis Drug Safety. So the advantage of a randomized clinical trial is that it would allow all patients to get the same treatment.

So in the trial that we propose, all patients would get ICS, have access to ICS, and have the Foradil on top of that. In SMART, we did see an imbalance in events among African-Americans. This would allow us to tease apart whether or not that was socioeconomic or perhaps beta2 polymorphisms.

As Dr. Pascoe mentioned, we would also do genotyping. In addition, we have done some database studies, including a Medicaid study, which we have just the preliminary results available, but that will give us more of a sense of how these events occur in the real world.

But in a randomized trial, we hope that the use of inhaled corticosteroids will help us get to these issues better.

DR. SWENSON: Dr. Platts-Mills?

DR. PLATTS-MILLS: I'd like to follow through on Mr. Mullins' question and put a question to Dr. Pascoe.

I welcome your stated intention that any study should provide new information and I would suggest that there really are two big overlapping

problems in the management of adolescent asthma in the United States.

The first is the fact that the mortality among African-Americans living in poverty is three or fourfold higher than it is in anywhere else, and that's a national disgrace to the United States. And, clearly, the primary issue that we ought to be addressing may be not the issue that we've been addressed to.

But the second issue is obesity. Obesity is the number one concern of childhood in the United States today and is increasingly overlapping with asthma. And it overlaps in lots of ways, but probably one of the biggest is that overweight children are all deconditioned.

If we test their VO2 max, they have declined in VO2 max and it's exactly the same in those who have been diagnosed with asthma and those who haven't. Thus, giving them a diagnosis of asthma and giving them an inhaled steroid, you enable the mother to then say, "You mustn't do exercise because it will make your asthma worse," and it's exactly the opposite

result than it should be.

So a question to Dr. Pascoe is, can you address any of these issues? Can you actually do studies in African-Americans living in poverty and address the issue of obesity at the same time?

MR. PASCOE: Thank you. Steve Pascoe from Novartis. It's important. I think they're very relevant questions. I think they're slightly disparate questions.

So I think, can you do studies in African-Americans, the answer is depending on the level of benefit and risk you want to exclude. So if you have a risk difference or rate ratio, whatever it is, that's gauged against the population you can incorporate, then I think that's fine.

One of the things that potentially makes it easier is if you believe the incidence of whatever your event of interest is a lot higher, then, clearly, your study becomes more manageable.

One of our concerns is that because the differences, we believe, are probably related to healthcare provision is that when you enroll people

into a clinical study, they actually start behaving like people who have a better healthcare provision.

So I wouldn't go into it believing that we are going to see the similar rates, and I think the GSK study we heard about earlier on actually showed rates that are in keeping with normal study populations.

So in relation to obesity, there are two questions here; one, whether treatment response is the same in obesity and whether administering therapy encourages obesity.

I've heard people argue that if you manage people's asthma, they will intrinsically exercise more and lose weight, and I've also heard the theory you put forward that it gives them an excuse not to exercise.

I think that's a different study than looking at a comparator study of treatments. It's looking at outcome of the effect of the intervention, which would take a different methodology; clearly, clearly, an intriguing question; clearly, something that I think would be very relevant and valuable to

explore.

DR. PLATTS-MILLS: In some of the control trials, obese patients are actually excluded. And maybe that's a question for all of you. Are obese patients excluded from your control trials? I mean, remember, we're facing 30 percent obesity in the United States within the next 5 years.

DR. SWENSON: Dr. Knobil? And I think these answers can be quite short.

DR. KNOBIL: No. We do not exclude patients from clinical trials based on BMI or weight at all. And we've looked retrospectively and we haven't seen a difference in response based on BMI, either, to ICS/LABA.

MR. PASCOE: Dr. Pascoe, Novartis. We don't put a cap on BMI.

DR. SWENSON: Dr. Andersson?

DR. ANDERSSON: No. It's the same thing. We never exclude high BMI.

DR. SWENSON: Dr. Joad?

DR. JOAD: I guess I have two questions. One, just as a follow-up to this, is how, in the case

control study, how you would pick the controls and all the things that would go in to picking a control or several controls or how extensive will the picking of the control be.

Then my other concern is about the pediatric dose of Advair being 150. If you follow the pediatric asthma guidelines, 100 is too low for medium and severe persistent asthma, and if you go through what you presented from the FDA prescribing information, it looks like 30 percent of the Advair prescriptions are for more than that and the Advair HFA are even more than that.

So people are clearly following the guidelines and not the FDA approval. So I'm concerned that a study will be done in pediatrics that won't be relevant for pediatricians or children.

Those are two completely different questions.

DR. CAMARGO: Sure. There were two, right? I'll take the first one. First off, thank you very much for asking me a question about my odds study.

DR. SWENSON: This is Dr. Camargo.

DR. CAMARGO: Dr. Camargo from Boston. So in response to your question, this is very preliminary what I'm proposing. It can certainly be modified. The initial thoughts of the working group were to match by age, sex, and year.

Beyond that comes the big questions about matching, in a sense, for the severity or lack of control or better than matching, maybe restricting. And Dr. Schoenfeld touched on that with the idea that we might also require, for instance, in a subset, that everyone is on an inhaled corticosteroid, that they've maybe had the same number of prescriptions filled in the last year.

This is the way you would start to tackle the issue of making the groups as similar as possible with severity so that the only difference between them, you would hope, would be whether one was on LABA or not.

But all of this is subject to discussion and we can look at it in many different ways to address many different concerns. Remember that all of those patients and all of their events and all of their

prescriptions, they already happened. The data are sitting right now ready for analysis somewhere. We have to pool them and to clean them. It's already out there, which is a big advantage.

DR. JOAD: But what about what we were just discussing, which is race, ethnicity, and obesity? Can you pool those things or not?

DR. CAMARGO: I think some of the datasets do have race as a variable, and, again, I specifically cited for Mr. Mullins the Medicaid, I think the DOD. And so we'd have to look at each of them to see how many of them had it. I know some don't have it. If we go back to an odds ratio of 4, that makes life a lot easier to see a signal.

In terms of BMI, some datasets have it, most don't and we know that. That's changing. Now, more and more people are including BMI as a fifth vital sign or what have you.

But I think, first, you commit to a course which is quite different from the one that we started out on this morning. And maybe it's complementary. Maybe it's the only one. But you first commit to go

in that direction and then you try to work out some of these issues. And I think there are solutions for them.

DR. SWENSON: Dr. Redlich? I'm sorry. We'll have one more response.

DR. KNOBIL: Kate Knobil, GSK. I'm not sure I can directly answer your second question. It seems more of a comment that some physicians are using their judgment to go to a higher dose of Advair for pediatrics.

DR. JOAD: No, the guidelines will take you higher than that. The NAEPP guidelines, if you follow them, 100 micrograms of fluticasone is not going to be a medium or a high dose for a child.

DR. KNOBIL: Agreed.

DR. JOAD: So it's not just they're doing it. They're doing it based on guidelines.

DR. KNOBIL: But it has to be based on their judgment, based on how the child is doing.

DR. JOAD: Right, and the severity of their asthma.

DR. KNOBIL: Right, right. So the data that

we have, really, we only have data with Advair 150. We have data to compare Advair 150 with doubling the dose of FP or higher and FP 250, which shows equal or better efficacy.

You've seen the BADGER results recently, too, which showed that patients were more likely -- children were more likely to have the best response to Advair versus FP 250.

Now, part of the benefit-risk is also whether or not you want to expose a child to a higher dose of inhaled corticosteroid because of the potential for growth effects and the like.

So we don't have any data comparing a higher dose of Advair to a lower dose of Advair in pediatrics. So, yes, the guidelines say that, but I don't have any data to support doing that. It's really up to the physician's judgment about how the child is doing.

DR. SWENSON: Dr. Redlich?

DR. REDLICH: It's a quick question. I was wondering if someone could clarify what the definition of an asthma-related death is. The SMART study had

two categories or several categories, but one was asthma-related death and then there was respiratory-related death, and I wasn't totally clear how that was defined.

DR. KNOBIL: Kate Knobil, GSK; I think you know that already. For SMART, an asthma-related death was determined by a committee that adjudicated each event. So we got the records together and a death certificate, if available, any records that would help determine whether or not the event was asthma-related.

So it was really the judgment of this three-member committee, looking at all of the data that were available, to be able to adjudicate that event.

Now, a respiratory-related event could be something that had to do with a respiratory condition, but was not asthma. So, for example, if the patient had a diagnosis of COPD, as well as asthma, and had a death related to that; if they had a pulmonary embolus, that could also be a respiratory-related event, but not asthma-related.

Does that answer the question?

DR. REDLICH: Yes. It seems that if you're

concerned -- and I think this point was raised by someone else -- if you're concerned about the severe adverse effects, then it would seem that all forms of adverse effects are a concern.

DR. KNOBIL: Yes. Well, we always collect severe adverse events in every study. So that's done as a matter of course.

DR. SWENSON: Dr. Rosenthal?

DR. ROSENTHAL: Thank you. Jeff Rosenthal. So I'm just thinking back to the discussion early this morning about the ethics of the proposed study and I'm reflecting, as well, on the sort of weak -- maybe weak is the wrong word -- the unequivocal benefit, risk-benefit balance of even combined therapy in the pediatric age groups.

So I guess my question is I'm wondering if people can reflect on whether there aren't particular ethical dilemmas with doing the proposed study in the pediatric group as a first step or should it be -- if we move ahead with the proposed study, should it be something that's limited to the adult age group, because peds are vulnerable and there seems to be more

question about the risk-benefit balance in that age group?

DR. PLATTS-MILLS: Which way around do you see the ethics?

DR. ROSENTHAL: Well, okay. The question is in which direction do I see the ethics. My concern is that if there are questions of the ethics of such a trial in the adult population, then there are even greater concerns about the conduct of such a trial in the pediatric population. That was the direction that I was intending to have things slant.

But I'm not actually making a statement so much as just raising this issue for some comment from people around the table.

DR. SWENSON: Do we have anybody that wants to at least make one or two comments to that question? All right. Dr. Joad?

DR. JOAD: There are a number of us who do pediatric pulmonary here and I think the combination of inhaled corticosteroids and LABAs is a standard that many of us and consider very important for our patients and it's more important to study it than not

to study it.

My concern about the dose was that we were going to under-dose them, not that we shouldn't study it. So I absolutely support a study in children.

DR. SWENSON: Dr. Fink?

DR. FINK: My comments will be very similar to Dr. Joad's. If we're already reliably using LABAs, pediatric pulmonologists, and to not study them would then leave us with less information about are we using them properly and are they safe to use in pediatrics than to study them.

DR. SWENSON: I have a question, and this would be to all the sponsors. I think we're concerned about this possible constant occupancy of the beta receptors in asthma.

In your trials, where you have looked at ICS versus LABA plus ICS, one fear I have is that perhaps all we're going to do is substitute one beta-agonist for another. Someone said the long-acting beta-agonists are just longer-acting short-acting beta-agonists.

So in your dataset, what is sort of the

total burden of beta-agonist use between these two groups and perhaps are we just going to see, in a trial going forward, that we will just see more albuterol use in the ICS group? And will we be basically studying almost two equal populations?

DR. KNOBIL: Kate Knobil, GSK. I'm not sure that I can give you a direct answer to the total burden, because it hasn't been calculated. It's something that we could look into and potentially have an answer for you tomorrow.

But one of the reasons why LABAs were approved in the first place as single agents is that they were compared with short-acting agents and they were significantly better in improving lung function and, in the case of Serevent, improving quality of life.

So when you look at the rescue use in those trials -- when I say rescue, I mean fast-acting albuterol use -- and those trials compared LABA or Serevent twice daily with albuterol 4 times daily, and also measured the extra albuterol use, there was significantly less fast-acting albuterol use in those

trials.

Going forward, in studies of ICS/LABA, we also see that same trend, that there is significantly less short-acting beta-agonist use when patients are using ICS/LABA than when they're using ICS alone.

That balance will differ depending on your patient population, though. So if you're bringing a relatively well controlled population, that difference may be smaller. If you're bringing in a less well controlled population, that difference may be larger.

So I don't know if it's possible to give you a specific answer about the beta-agonist burden. Did you have any other clarifications?

DR. SWENSON: No, no. I just wanted you to try to address that issue. And I agree with the symptoms, but we're not so much concerned at all or even arguing with symptom control. We're worried about this much, much rarer problem of adverse events.

DR. KNOBIL: That's right. Yes. Right. But symptoms are directly related to how often a patient uses their short-acting beta-agonist. So it's hard to tease those things apart.

DR. ANDERSSON: Tomas Andersson, AstraZeneca. Could I have the backup slide, please, on lung function from my main presentation? Maybe not.

Well, in my main presentation, I showed the picture of lung function being improved and maintained compared to budesonide alone in clinical studies, and that's probably well known.

The main efficacy of lung function, it's well known, in all the studies where we use formoterol together with budesonide, lung function is maintained and the improvement doesn't wane off with time.

This is one study that Cathy Bonuccelli showed at the beginning and what you see here to the right is that either if you look at day of randomization or end of treatment, you have exactly the same benefit when formoterol is used together with ICS.

If you use formoterol alone, then the effect on lung function, the bronchodilatory effect decreases over time. So I think, in practice, in clinical situations, the tolerance of the beta receptor is not a practical clinical problem.

Also, the other thing I was going to say is that in clinical studies, where patients are randomized either to ICS/LABA or ICS alone, they are free to use their reliever, it's not just they need, and the reliever is typically a short-acting beta-agonist.

Even if they keep on using that as much as they can in the ICS group, they still don't reach the lung function levels they do in the combination treatment arms.

So I don't think, in clinical practice, you achieve what you can achieve with formoterol and ICS when you add a SABA to an ICS. You just don't get the efficacy. At least patients don't use their reliever enough in the comparator group, if you see what I mean.

DR. SWENSON: Dr. Mouton?

DR. MOUTON: I just want to go back just a second to ask the sponsors. I was just curious why, given the concern over the African-American subpopulation, there wasn't a planned subgroup analysis presented as part of your trial designs and

if so, what effect would that have over the overall sample size and recruitment timelines that you propose.

MR. PASCOE: Steve Pascoe, Novartis. I'm sorry if it didn't come across, but our proposal was that we would enrich the population and would collect data. Our concern is in the study alone, the subgroup would be too small.

So our proposal would be that we build in, if there's more than one study that's going to be conducted, a common thread for African-Americans. Then we can life an analysis out from the combination of studies.

DR. MOUTON: Well, why build it if it's going to be too small to start with?

MR. PASCOE: Say we have a third of the required numbers in our study, then if each study has that same problem, the combination of the studies would meet the required numbers.

DR. MOUTON: So you're looking for all sponsors to help you meet that burden.

MR. PASCOE: I think it would be a feasible

way to address the problem.

DR. MOUTON: I had a second question that was regarding -- there was a mention of looking at the beta-agonist receptors and it sounded as if you were saying that you were going to look at genetic markers in African-Americans.

I was just wondering, given that we know that African-American is really a social construct, how do you propose to look at that in terms of genetic markers?

MR. PASCOE: So I think the key is defining what we mean by African-American, and I think if you move towards a construct, a definition where it is a social construct, then the clarity of genetic differences, I think you're absolutely right, are very much more blurred.

I think if an approach is taken when you can more accurately define a separate ethnicity, then probably any genetic differences will be identifiable.

DR. MOUTON: Well, I just wanted to point out that the NASA Human Genome Center has already looked and found that 99.9 of the phenotype is across

the population. There's more similarities with my colleagues here and here than in terms of a genetic phenotype. Only .1 percent of the genome is explaining phenotype. So I think race is a social construct.

MR. PASCOE: No. I think I absolutely agree with your numbers. I think you're spot on. I think there have been questions because of the beta2 receptor differences with beta antagonists in hypertension; that because of the SMART study and the concurrent studies, the question was, could this be an explanation.

I don't think there's advocacy of it being an inherent difference, but a question to be answered.

DR. SWENSON: Dr. Bonuccelli, did you want to say something either in regards to that or a previous question?

DR. BONUCCELLI: Boy, the heels aren't tall enough. I just wanted to answer the first question, that we would definitely do subgroup analyses. But I also wanted to remind the committee that we have a greater than 700-patient trial in African-Americans

that we think we'll report out this year, intended to look at safety.

DR. SWENSON: Dr. Andersson?

DR. ANDERSSON: Tomas Andersson, AstraZeneca. Yes. Just to point out what has already been said, those 720 patients took 22 months to recruit, just giving another indication of how difficult it is to recruit a large sample.

I would, however, like to invite Dr. Bleeker to comment on the genotype variability and how that can affect the safety. It's the heterogeneity of the beta receptor that is the focus of this discussion and I think that we now have plenty of data to address this question.

DR. BLEEKER: Dr. Swenson, I guess I need to say something about conflicts, which may be longer than my answer. But I'm a professor of medicine, pediatrics, and genomics at Wake Forest and I direct the Genomics and Personalized Medicine Center.

I'm here as a consultant, and I'm being paid for that, of AstraZeneca, and I've also consulted on this meeting with GSK, and, in the past, in terms of

drug development, have consulted with a number of other companies, Merck and Novartis.

Our group also does clinical trials, all administered through Wake Forest, on drug development and these are trials for which I don't receive direct salary. And, finally, I'm either PI or co-PI on a number of NIH grants that look at asthma severity, pharmacotherapy and pharmacogenetics, and I do receive salary from those.

You bring up some interesting comments on genomics of the beta receptor. If we go back to perhaps the 2005 review, there were questions that were left in terms of whether common variation in the beta receptor may alter response to therapy.

One of the problems with a number of the earlier trials, from a genomics or genetics point of view, they're too small to answer the question adequately.

There are three trials with SABAs, short-acting beta-agonists, which do say when they are used regularly, there may be diminished response or a worsened response in individuals who are of an

arginine/arginine homozygote genotype.

Subsequent to that, the NIH/NHLBI/ACRN study did a retrospective study of that with LABAs and saw some effect, and now there have been at least four major studies published with this; one in Lancet of an analysis, a retrospective analysis of a little over 2,000 individuals who are on combination therapy.

It was both a combination of budesonide with formoterol and a combination therapy of salmeterol with fluticasone and did not see, in almost 350, an effect of arginine/arginine on response to therapy, which included improvement in lung function and exacerbations over a 7-month period. Other variation in the gene was looked at and it didn't interact.

Subsequent to that, in the last month or so, two papers have been published, one from the Asthma ACRN/NHLBI Network in Lancet, and this was a prospective genotype stratified trial of homozygotes, arg-arg, and gly-gly. They didn't see an effect on lung function.

There may be was less of an improvement in arg/arg individuals in hyperresponsiveness, and that's

something that needs to be followed. The other is a study sponsored by GSK, which is now published in the American Journal of Respiratory and Critical Care Medicine, of 590 people, looking both at combination therapy and salmeterol alone and didn't see an effect due to arg/arg genotypes.

The only proviso on this is when we talked about ethnic differences, there are different or more variation in different ethnic groups. In African-Americans and people of African dissent, and this is being looked at intensively by other NHLBI studies in terms of asthma severity in our severe asthma NIH population and in larger populations funded in grant opportunity grants, how this variation differs and how it may affect response.

The other area of interest as we are looking down the line is whether rare variants may have an effect, and that is something that's worth considering at some point, and these are very rare variants that occur in less than 1 percent of the population.

DR. SWENSON: Well, we've reached the end of the day here and I think with that as our last

discussion, we will meet again tomorrow morning at 8:00 a.m. Thank you very much.

[Whereupon, at 5:05 p.m., the meeting was concluded.]